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Editors

Antibiotic Policies

Controlling Hospital Acquired Infection

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Dr. Ian M. Gould
University of Aberdeen
Medical School
Foresterhill
AB25 2ZD Aberdeen
United Kingdom
i.m.gould@abdn.ac.uk

Prof. Jos W. M. van der Meer
University Hospital Nijmegen
PO Box 9102
6500 HC Nijmegen
Netherlands
J.vanderMeer@aig.umcn.nl

ISBN 978-1-4419-1733-1 e-ISBN 978-1-4419-1734-8
DOI 10.1007/978-1-4419-1734-8
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011936235

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Healthcare-associated infections (HAIs) are an increasing problem worldwide and need to be addressed urgently. In the European Union, about 7% of patients in acute care hospitals experience HAIs; recent analysis discloses an even higher prevalence in developing countries. The international contributors to this book, in drawing on their considerable experience in different settings, perform an important function by clarifying the main issues for tackling HAIs. Their assessment necessarily covers both the characteristics of the principal pathogens and the key organisational and operational factors implicated for hospitals and their staff. This detailed analysis is accompanied by discussion of best practice for preventing and managing the challenges presented by HAIs. I welcome the emerging perspective from this book that emphasises that the options for antibiotic policy must cover a broad range of activities. There are policy issues to face for surveillance, for prudent and responsible prescribing, for developing and implementing guidelines for infection control, and for raising awareness of the threat of HAIs throughout the medical profession and with patients.

The present volume is very valuable in communicating strong messages concerning the nature of the burden to individuals and to health systems, but also about the opportunities for change to improve patient safety. From my own experience with Academies of Science across Europe (who, as the European Academies Science Advisory Council, have also reported on some of these issues, www.easac.eu), I know that there is still much to be done to engage with decision-makers at all levels about these matters.

I am also convinced that there is an urgent requirement to increase collective commitment to biomedical research and innovation because otherwise the longer-term battle against HAIs and associated antibiotic resistance will be lost. We need this research—integrating epidemiology, social and biomedical sciences—so that we can better understand the behaviour of both microbial and human populations. Moreover, we need to become more adept in translating the research advances into faster development of novel, improved, diagnostics and therapeutics and their use in new and better ways.

To be effective, therefore, public health policy for the use of those antimicrobial agents presently available to us must be well coordinated with innovation policy.

In addition, strategy for human health must be aligned coherently with strategy for veterinary health. The common element in developing all of these policies is the reliance on robust, validated evidence. Taken together, the individual contributors in this book, assembled by insightful editors, play a vital role in collating that definitive evidence and assessing its implications, notwithstanding the inevitable uncertainties occasioned by the rapid pace of change in burden of infection and the varying experience in different countries. This book serves a twin purpose in helping to construct a more informed evidence base for coherent policy making while, at the same time, providing practical advice for health professionals in the prevention and control of HAIs.

Volker ter Meulen
Past president of European Academies Scientific Advisory Council (EASAC)
Past president of the Leopoldina

Contents

Contributors

G. De Angelis Department of Infectious Diseases, Università Cattolica, Rome, Italy
e-mail: etacconelli@rm.unicatt.it

Abhijit M. Bal Consultant Microbiologist and Honorary Clinical Senior Lecturer, Crosshouse Hospital, NHS Ayrshire and Arran, Lister Street, Kilmarnock KA2 0BE, Scotland, UK
e-mail: abhijit.bal@nhs.net

Eimear Brannigan Hammersmith Hospital, 2nd Floor Hammersmith House, Du Cane Road, W12 0HS London, UK
e-mail: eimear.brannigan@imperial.nhs.uk

Yehuda Carmeli National Center for Infection Control, Israel Ministry of Health, 6 Weizmann Street, 64239 Tel Aviv, Israel

Division of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
e-mail: mitchells@tasmc.health.gov.il

Matthew E. Falagas Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 15123 Marousi, Athens, Greece
e-mail: falagas@tufts.edu, m.falagas@aibs.gr

Hellen Gelband Center for Disease Dynamics, Economics and Policy, 1616 P Street, NW, Suite 600, Washington, DC 20036, USA
e-mail: gelband@cddep.org

Evangelos J. Giamarellos-Bourboulis 4th Department of Internal Medicine, ATTIKON University Hospital, 1 Rimini Street, 124 62 Athens, Greece
e-mail: egiamarel@med.uoa.gr

A. Goorhuis Department of Medical Microbiology, Leiden University Medical Center (LUMC), Albinusdreef 2, 2333 ZA, Leiden, The Netherlands
e-mail: E.J.Kuijper@lumc.nl

Ian M. Gould Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, AB25 2ZN Aberdeen, Scotland
e-mail: i.m.gould@abdn.ac.uk

Stephan Harbarth Infection Control Program, Geneva University Hospitals & Medical School, 1211 Geneva 14, Switzerland

Peter M. Hawkey School of Immunology and Infection, University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK
e-mail: peter.hawkey@heartofengland.nhs.uk

Yoshiro Hayashi The University of Queensland, UQ Centre for Clinical Research, Herston, Brisbane, Australia
e-mail: y.hayashi@uq.edu.au

Royal Brisbane and Women's Hospital, Department of Intensive Care Medicine,Herston, Brisbane, Australia

Alison Holmes Hammersmith Hospital, 2nd Floor Hammersmith House, Du Cane Road, W12 0HS London, UK
e-mail: alison.holmes@imperial.ac.uk

S. Johnson Departments of Research and Medicine, Hines Veterans Affairs Hospital and Loyola University Medical Center, Chicago, IL, USA

Ed J. Kuijper Department of Medical Microbiology, Leiden University Medical Center (LUMC), Albinusdreef 2, 2333 ZA Leiden, The Netherlands
e-mail: E.J.Kuijper@lumc.nl

Kevin Outterson Boston University School of Law, 765 Commonwealth Avenue, 1140, Boston, MA 02215, USA
e-mail: mko@bu.edu

David L. Paterson The University of Queensland, UQ Centre for Clinical Research, Herston, Brisbane, Australia
e-mail: david.antibiotics@gmail.com

Mitchell J. Schwaber National Center for Infection Control, Israel Ministry of Health, 6 Weizmann Street, 64239 Tel Aviv, Israel
e-mail: mitchells@tasmc.health.gov.il

Evelina Tacconelli Department of Infectious Diseases, Università Cattolica, Rome, Italy
e-mail: etacconelli@rm.unicatt.it

Jos W. M. van der Meer Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
e-mail: J.vanderMeer@aig.umcn.nl

Paschalis Vergidis Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

M. H. Wilcox Department of Microbiology, Old Medical School, Leeds General Infirmary, Leeds, UK

Cara Winters 3644 N. 52nd St, Phoenix, AZ 85018, USA

Olga Yevtukhova Boston University School of Public Health, 715 Albany Street, Talbot Building, Boston, MA 02118, USA

Introduction

Hospitals, by their very nature, are dangerous places. Sick and infected patients are clustered together in one institution, often in close proximity to those who are immunosuppressed due to recent surgery, chemotherapy or transplantation. Contact between these various patient groups is easily achieved via the hands of healthcare workers (HCWs), use of shared equipment or the hospital's air handling system. Thus, for many virulent pathogens, hospitals can effectively act as a giant PCR machine, rapidly multiplying the number of resistant isolates encountered, but with no need for Taq polymerase. Until recently, the key focus of many health bureaucracies has been primarily on the quantity of healthcare—namely patient throughput, hospital length of stay and size of patient waiting lists. It is only in recent years as hospital-associated infections have become increasingly common and more difficult to treat, that there has been a greater emphasis on healthcare quality—particularly in terms of limiting the emergence and spread of antimicrobial resistant pathogens.

Overall, progress in understanding and successfully controlling healthcare-associated infections (HAIs) has been painfully slow. Although many of the important issues associated with antimicrobial resistance were nicely summarised in the 2001 World Health Organization (WHO) report—"WHO—Global strategy for containment of antimicrobial resistance" [1], the public release of this important document was an unfortunate disaster, with its long-scheduled US public launch being only 30–60 min after the first terrorist attacks on the World Trade Center on 11th September 2001. Thus, this strategy received little public attention and in the months that followed with the subsequent, but unrelated, anthrax attacks, tens of thousands of Americans, instead of limiting their antibiotic use, were given prolonged courses of ciprofloxacin and other agents as post-exposure prophylaxis [2]. Nevertheless, many of the issues raised in this important WHO strategy remain highly relevant today. The problem, however, is that the severity of the antimicrobial resistance issue has increased dramatically during the past 10 years since 2001, such that what was previously a storm cloud on the horizon is now a cyclone/hurricane directly affecting patient care and outcomes.

In broad terms, there are two means by which patients can develop multi-resistant infections—they can either develop their own resistant pathogen, or they can acquire someone else's strain.

Emergence of new resistant pathogens is directly related to antimicrobial selection pressure either via the mutation of new resistance genes or the alteration of bacterial ecology (e.g. in the gut) that facilitates the transfer of naturally occurring or emergent resistance genes from one bacterial class to another. The use and misuse of antibiotics is intimately involved in both these mechanisms—particularly if antibiotic dosing is inappropriately low such that Darwinian selection of resistant strains is facilitated. Of course, antibiotic use in food production can have the same effect as direct human antibiotic misuse, since it can select for both resistant pathogens (e.g. fluoroquinolone-resistant *Campylobacter* in chicken meat) or resistance genes such that food consumption results in either direct fecal colonisation or acquisition of resistance genes by routine gut flora [3, 4]. Antibiotic stewardship is therefore not simply a hospital issue.

Cross-transmission of resistant pathogens between patients is a relatively simple process in many hospitals and is therefore a key focus of hospital infection control initiatives. However, supposedly simple concepts such as improved hand hygiene and reliable cleaning of shared hospital equipment and the hospital environment have proven difficult to implement in practice, largely because they require a change in human behaviour [5–7]. Culture-change programs in healthcare are time-consuming, expensive, non-glamorous and require ongoing maintenance to be effective and result in sustained behavioural change. Nevertheless, programs such as the "*WHO Patient Safety: Clean Care is Safer Care"* is a good example of where effective culture-change in terms of improved hand hygiene compliance (with increased use of alcohol-based hand-rub) can have a major impact on rates of nosocomial infections [8].

Issues related to hospital design are also crucial to limiting transmission of resistant pathogens. The ideal hospital would probably consist entirely of single-bed rooms, each with an ensuite bathroom. Simple infection control axioms such as "one bum per toilet" seem obvious if one aims to limit disease transmission, but are rarely implemented in practice—generally because of perceived increased costs. Yet, the advantages of such a hospital design would be the ready physical separation of infected from non-infected patients and potential savings (both human and financial) in preventing hospital-associated infections [9, 10].

Within hospitals, appropriate antibiotic prescribing is paramount. However, successful antibiotic stewardship programs are not necessarily easy to implement and generally depend on the presence of senior Executive commitment to the program, clearly defined (preferably evidence-based) antibiotic prescribing guidelines and an effective system of monitoring and oversight [1, 11, 12].

It is in this broad context of rapidly emerging and widespread antimicrobial resistance that this text **"*Antibiotic policies: controlling hospital-acquired infection*"** is so relevant, since it concisely aims to summarize the current situation regarding antimicrobial resistance, both in terms of the general policies needed for control and the specific issues related to key multi-resistant pathogens.

M. Lindsay Grayson

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Healthcare Associated Infections—The Size of the Problem

Eimear Brannigan and Alison Holmes

Abstract The global burden of healthcare associated infections (HAI) is currently unknown, despite international efforts to fill this gap in our knowledge. Where the size of the burden of HAI has been quantified, the greatest impact is in those countries with least resources to measure and manage them. Across industrialised nations where surveillance systems exist, the challenges are of targeting resources, achieving harmonised definitions of HAI, choosing which processes and outcomes should be measured, and the target audience for reporting of results either within the healthcare setting or to external scrutiny. HAI have additionally come into use as performance indicators, promoted as part of the patient safety agenda, and, together with the arrival of a 'zero tolerance' approach for preventable HAI, these have led in some centres to financial sanctions for failure to prevent. The consequences of these developments remain to be determined.

Keywords HAI • SAB • MRSA • UTI • VAP • HAP

Introduction

Since the publication of the findings of the Study of the Efficacy of Nosocomial Infection Control (SENIC) (Haley et al. 1985) first highlighted that healthcare associated infection (HAI) posed a significant healthcare challenge, all involved in delivery of healthcare in the US and further afield have grappled with how to best manage infections acquired during exposure to healthcare. In addition, since systems of measuring infection processes linked to outcomes with feedback to those delivering the care have been shown to improve practice and reduce infections (Haley et al. 1985), these have been adopted in the developed world and used as performance indicators to drive quality improvement in infection prevention. Such systems, and the urge to 'aim for zero' referring to preventable infections, have become central to the patient safety agenda, with implications for healthcare outcomes, patient safety and healthcare economics.

E. Brannigan (✉)
Hammersmith Hospital, 2nd Floor Hammersmith House, Du Cane Road, W12 0HS London, UK
e-mail: eimear.brannigan@imperial.nhs.uk

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_1, © Springer Science+Business Media, LLC 2011

Size of the Global Problem

It remains true that while there have been advances in healthcare systems and technology relevant to prevention of HAI, in much of the world, no measurement or recording of HAI occurs and thus the 'size of the problem', although estimated to be large, is unknown. This is true of many developing world settings.

HAI occur wherever healthcare is delivered, making identification and definition of preventable infections and implementation of prevention practices a global problem. However, the actual size of the problem of HAI is unknown, and estimates of global HAIs are acknowledged to be limited by lack of reliable data (Allegranzi et al. 2007). 3.5–10.5% of hospitalised patients in industrialised countries may experience HAI (E.C.D.C. 2008), while greater than 25% of hospitalised patients in developing world nations may be affected (W.H.O. 2005). Data from developing world settings are scarce, but multicentre studies in a small number of countries (Rosenthal et al. 2008, 2010) indicate rates between 5 and 12%, while virtually no data exist on HAI in the most resource limited settings. A recent review illustrated the discrepancy in representation between World Health Organisation (WHO) regions amid the published literature on HAI, with Africa and the Western Pacific in particular poorly studied (Allegranzi et al. 2011).

Global Challenges to HAI Prevention—Discrepancies in Healthcare Facilities' Resources

In the most resource limited healthcare settings, formal infection control policies and programmes do not exist as these societies have more pressing priorities which may include political unrest, poverty, natural disasters or war. In such cases, basic needs like clean water and adequate sanitation are not available, and any consideration of the additional needs required for the delivery of healthcare including consistent electricity supply, clean equipment, and facilities for sterilising equipment and instruments for procedures is a luxury. Family members, rather than trained healthcare workers, may be key carers during a hospitalisation, providing funding for medication and equipment, in addition to nursing care and feeding. Prevention of transmission of infection in general and enteric infections in particular, is often impossible because effective hand hygiene is not readily achievable. Many such centres do not have basic diagnostic laboratory facilities, and currently used laboratory-based definitions of HAI would not be suitable for such centres. The scale of the problem of HAI in such settings goes beyond that of not achieving control, and HAI numbers and rates must be considered to be large as the resources for prevention are extremely limited (Raka 2009). Here there are no HAI data collection systems, no routine surveillance, and no targets for reduction of HAI rates.

Blood and Injection Safety

Blood-borne virus transmission is not infrequent via healthcare routes in such settings, where transfusion and injection safety are absent (W.H.O. 2005). While in 2000, 70 countries did not screen donated blood for HIV, hepatitis B or hepatitis C, currently the risk of bacterial infection from transfusion is greater than the risk of acquiring these viruses. Reuse of contaminated needles or syringes during injections in limited resource settings poses a major threat for transmission of infection, accounting for an estimated 21 million hepatitis B infections, 2 million hepatitis C infections and over 95,000 HIV infections. Percutaneous injury of healthcare workers, and indeed exposure of patients to infected healthcare staff remain significant risks in healthcare in much of the world. Occupational health screening of staff to protect staff and patients, as well as systems for tracking immunisations of staff and their deployment are challenging throughout healthcare, not only in resource limited settings.

In a growing number of transitional healthcare settings around the world, healthcare is much safer, with clean water and cleaning processes recognizable as comparable to those in the industrialised world, and with some form of infection prevention and control (IPC) training included in staff education. Hand hygiene is possible with both hand-washing and alcohol hand-rub availability, and engagement with hand hygiene initiatives, like the WHO global hand hygiene challenge (Allegranzi et al. 2007). Some measurement of quality of care, and of healthcare outcomes may be performed and used to identify areas for improvement in practice.

Only in a small fraction of the world's healthcare facilities do patients have access to single-use sterile instruments and supplies, are there good quality reprocessing facilities and is there abundant electricity and clean water. In these facilities, well-trained staff are expected to engage in IPC activity, and the culture of infection prevention and control as the responsibility of all staff is promoted. Laboratory accreditation is a requirement in such centres, and institutional accreditation and inspection often occur. Complex HAI surveillance systems are employed, and these are often used not only for local quality improvement efforts and as alerts to breakdown in infection control measures, but also for external reporting of infection rates or numbers. This may be as a national or regional mandatory requirement as for MRSA bloodstream infections in England and Wales, and in certain US states which mandate public reporting of a variety of nosocomial infections (Edmond and Bearman 2007); or public reporting may be as part of a voluntary reporting system, as has long been traditional in England, and for example pertained to meticillin-sensitive *S. aureus* BSI until December 2010. (H.P.A. 2010).

Institutions may use such reporting mechanisms to benchmark their practice against similar organisations. Despite the resources and sophistication in healthcare settings in industrialised nations, it remains difficult to achieve an apparently simple objective such as performance of effective hand hygiene by busy healthcare workers on each and every relevant occasion (W.H.O. 2005). Here the challenge relates to implementation of measures known to be effective in infection prevention, and

there is an increased promotion of multi-modal prevention activity, an example being the use of care bundles, in the insertion and ongoing management of invasive devices (Pronovost et al. 2006), and having the institutional structure and leadership to implement such tools remains challenging, such that preventable HAI continue to occur.

Measuring HAI in Limited Resource Settings

While HAI incidence in the developed world ranges between 5–11% (Allegranzi and Pittet 2007) in the developing world the incidence is estimated to range from 5–19%. This higher incidence is seen not only in overall figures, but also when, for example, device associated HAIs are examined, where the risk of HAI can be from 2–19 times greater than that seen in the developed industrialised nations (Arabi et al. 2008).

Despite the limited resources in some healthcare settings, it has been possible to establish targeted HAI surveillance. Where these studies have been performed, they have focussed on high risk settings, such as critical care, or on infections which have a well-established definition widely used in the developed world (Rosenthal et al. 2010). Thus, multicentre adult ICUs in centres across Argentina, Brazil, India, Mexico, Tanzania and Kosova, for example, have overall HAI rates of between 12.3% (in India) and 68.7% (Kosova) (Lynch et al. 2007). Among 22 prevalence studies and 12 incidence studies of HAI in a variety of populations in developing countries, prevalence was 5.7–19.1 per 100 patients and incidence 1.7–23.6 per 100 patients (Allegranzi et al. 2011). Caveats in interpretation include the high level of heterogeneity between studies included in this review and the low number of studies meeting pre-determined criteria for high quality.

International Nosocomial Infection Control Consortium (INICC)

The INICC study group, modelled on the United States' National Nosocomial Infection Surveillance (NNIS) system, was founded in 1998 in Argentina and supports developing world centres in establishing and maintaining a prospective HAI surveillance system (Rosenthal et al. 2008). In their most recent report, this group focussed on device associated infections (DAI), using NNIS definitions, to permit comparisons of rates between the participating developing world centres and those US centres involved in NNIS. While device-utilisation rates in developing world centres mirrored those in the US centres, the associated DAI rates were several times greater than those in the US (Rosenthal et al. 2010). Such data permits identification of the areas of highest priority for local action in prevention and reduction of HAI, and INICC supports the participating centres in targeted

interventions and training in application of infection control guidelines to achieve this end.

Developed World—The Size of the Problem

Industrialised nations may have the resources and technological infrastructure to support HAI surveillance as well as the training of staff in prevention of transmission of infection, but have adopted different methods to achieve this, use different definitions and record different HAI outcomes. The major challenges are the harmonisation of methodology and definitions, and the setting of priorities for prevention practice.

Size of the Problem in United States of America

HAI are recognised as among the most common adverse outcomes from hospitalisation in the US; approximately 1.7 million HAI are reported across the US each year, which are associated with around 99,000 deaths per year. Around a third of HAI are urinary tract infections, one fifth are surgical site infections, 15% are pneumonia and 14% are bloodstream infections (C.D.C. 2010).

Public reporting of HAI is not mandatory in all US states, but an increasing number are legislating for or considering introduction of mandatory reporting of HAI (Edmond and Bearman 2007). Although there has been no national data collection since the SENIC study, the CDC has been collating hospital surveillance data since 1970 from voluntarily participating sites, through the National Healthcare Safety Network (NHSN), formerly NNIS. The evolution from NNIS to NHSN also followed a change in focus from hospital-wide surveillance through more focussed surveillance on high-risk healthcare settings such as intensive care or surgery. The latest report includes data from 1545 centres across 48 US states, and these are aggregated into a single national database for purposes that include monitoring numbers and trends in HAI (Edwards et al. 2009). Data was submitted to the device-associated module, or to the procedure-associated module which includes surgical site infections and post-procedure pneumonias. Central-line associated bloodstream infection (CLABSI) rates (number of infections/number of line days × 1000) ranged from zero in small numbers of maternity and labour ward settings through 3–3.3 CLABSI/100 central-line days in paediatric medical, surgical, cardiothoracic critical care and inpatient settings and up to 5.5 CLABSI/1,000 central-line days in burns critical care units. Pooled mean rates of urinary catheter associated infections were highest among patients in rehabilitation, burn units, and neurology centres, 14.4, 7.4 and 7.4 infections/1,000 catheter days respectively. This was despite the lowest catheter utilisation ratios among rehabilitation patients.

Among surgical patients, highest post-operative pneumonia pooled means were among heart transplant recipients, or those undergoing splenic, or cardiothoracic procedures. Surgical site infections (SSI) per 100 operations among those most frequently performed, namely cardiac surgery (over 100,000 procedures over the study period), ranged from 0.35 to 8.49 according to the risk index category, increased risk correlating with increased occurrence of SSI. Hip and knee prosthesis surgery by contrast had low rates of SSI, between 0.58 to 2.4 SSI per 100 procedures, despite these categories of surgery being performed with similar frequency to cardiac surgery.

The NHSN continues to grow with the involvement of and reporting from smaller centres, since the opening of NHSN enrolment to all hospitals since 2007, and introduction of mandatory reporting laws in additional US states. This influx of participants, along with definition changes for reporting of CLABSI for example, may have influenced some of the pooled outcomes, for catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP) and CLABSI. As increased numbers of centres begin reporting to NHSN to fulfil their requirement to report HAI outcomes as relates to reimbursement, this network will be increasingly able to characterise national trends in risk to hospitalised patients.

Size of the Problem in Europe

Estimates in Europe are that approximately 4.1 million patients per year experience HAI, and that attributable deaths are of the order of 37,000 per year (E.C.D.C. 2005–2010). No aggregate data for HAI exist for all of Europe, but the most frequent infections are urinary tract infection (UTI) (27%), followed by respiratory infections (24%), SSI (17%) and bloodstream infection (BSI) (10.5%). The remaining sites of infection are predominantly gastrointestinal, mainly *C. difficile* infection (CDI), followed by skin and soft tissue infections and central nervous system infection.

European national prevalence studies indicate a HAI prevalence of 3.5–10.5% (E.C.D.C. 2008). These figures are gleaned from individual national prevalence studies within Europe, rather than any concerted data collection. However, there are collaborative efforts across Europe and currently agreed definitions are in use and permit comparisons of rates of selected HAI, namely SSI and nosocomial ICU infections across participating centres (Wilson et al. 2007). Methodological harmonisation has been achieved to a high level between the countries involved and has been implemented in the majority of European Union (EU) Member States. 15 networks from 12 European countries contributed to this network in 2007, accounting for over 260,000 surgical procedures and over 1100 hospitals, with the largest numbers reported from centres across UK, France and Germany (E.C.D.C. 2008). As Wilson notes, inferences from these data relating to quality of care are fraught with difficulty, including differences between participating centre case-mix, report-

ing of events and length and intensity of follow up. The challenge for Europe is to further extend existing surveillance of HAI across all EU member states, a diverse range of nation states with a range of infrastructures and resources (Fabry et al. 2007).

Size of the Problem Outside EU and US

Outside the EU and US there is relatively sparse data on HAI. Healthcare systems are relatively poorly developed from an organisational perspective in Australia, according to at least one author (Ferguson 2009), despite the existence of a sizeable HAI problem, around 177,000 HAI per year. In China, a developing nation with a rapidly growing economy systems for surveillance for HAI are also relatively poor, and as one of the most populous nations of the world, it is likely that the numbers are large, even if the proportion of hospitalised patients acquiring HAI is less than that in industrialised nations. Point prevalence surveys across 13 hospitals in a single province in China identified a HAI rate of around 4%, using definitions developed in China's Ministry of Health (Xie et al. 2010), which are modifications of CDC definitions. Respiratory tract infections were the predominant category of HAI (63.5%), followed by surgical site infections representing 9.6% of HAI, and then urinary tract infections (8.6%). Many HAI were diagnosed based on clinical and radiological criteria, while only a third had laboratory-confirmed cultures of a pathogen. A number of additional limitations of this work are acknowledged by the authors, and highlight the hazards of making comparisons between surveillance data with even slight differences in definition.

Comparing Nosocomial Infection Rates

The work of the International Nosocomial Infection Control Consortium (INICC) in supporting developing world centres in Latin America, Asia, Africa and Europe to collate targeted surveillance data using Centres for Disease Control and Prevention definitions reveals the advantages of common definitions across centres. Device usage rates were similar to those in US NHSN hospitals, but average infection rates were markedly higher. For example CVC associated BSI pooled rate for the INICC countries was ~7, almost threefold higher than that in US ICUs. The training and support in data collection the INICC group provides its collaborating centres should minimise the potential variability in observations, measurements and follow up, and so these comparisons are robust and can be used directly to understand where the requirements for improvement exist, and how best to focus prevention interventions.

The choice of whether to include only the first or all infection episodes in surveillance data, whether an ICU exposure is counted until the infection occurs, or throughout the patient's stay, as well as differences in case finding, length of follow

up or different post-discharge surveillance methods, ability to correct for case mix, or changes in case mix over time, can all have a significant impact on infection rates that renders comparisons between centres or networks of centres meaningless. The institution's attitude and culture regarding reporting adverse incidents including HAI can significantly affect how these are presented for public scrutiny and benchmarking. Validation studies, usually not routine components of surveillance, would assess real differences between case definitions against a common standard, but have cost and staff resource implications.

In Europe, development of a common case definition for *C. difficile* infection (Vonberg et al. 2008), extending existing surveillance across a larger range of centres, and into other HAI is a major challenge (E.C.D.C. 2008). This may be compounded by the need to increasingly focus on certain patient cohorts, for example the overweight, or obese who may be a greater risk of HAI (Falagas and Kompoti 2006) and respond differently to infection than non-obese patients (Falagas et al. 2009), or on neonates, a group relatively under-represented amid the HAI literature (King 2010). Although neonates and paediatric patients are usually not included in HAI surveillance, both the prevalence surveys from Hubei province (Xie et al. 2010) and the latest summary from NHSN (Edwards et al. 2009) capture data on these vulnerable patient groups in a move away from previous standards.

Prevention on a Global Scale—Global Patient Safety Challenge

In 2008 in Uganda, the Infection Prevention and Control Africa Network (IPCAN) was formed, and now has representation from 24 African nations; this network had its origins in improving safety of injections and of stocks of donated blood, but seeks to 'establish support in training, operational research and high standards of healthcare practice in healthcare facilities under one umbrella' (I.P.C.A.N. 2010).

The WHO global patient safety campaign encompasses these elements of safe injections and blood but also water and waste management safety, safety of clinical procedures and effective hand hygiene. Its champions promote strong national leadership and political commitment to stating these as priorities for healthcare systems, sustainability of system changes and raised awareness of national populations regarding these elements of raised standards in healthcare.

Preventable Infections

The reported range of preventable infections among HAI is between 10–70%, and the range of preventable SSI is 40–60%. In response to the realisation that certain infections, particularly those related to invasive devices, may be preventable, in some jurisdictions of the industrialised world, financial penalties will apply to insti-

tutions where a preventable HAI has occurred (Stone et al. 2010; Brown et al. 2009). The intention is to provide an incentive for improvement of quality of practice, but there is the potential for unintended consequences such as distortion of reporting and other behaviour (Carlet et al. 2009) which may negatively influence the size of the problem. There is ongoing debate regarding aspects of various HAI indicators, the intended audience, the systems for data collection and analysis, which has led to countries adopting different solutions (Haustein et al. 2011).

Sanctions for Failure to Prevent

In the US in 2009, the estimated excess cost of HAI across the nation was 28–45 billion dollars annually (Stone et al. 2010). Global financial constraints have led, through the US Deficit Reduction Act, to changes in reimbursement by Centres for Medicare and Medicaid Services (CMS), such that payment to hospitals will be denied for claims for selected conditions that occurred during a hospitalisation that were not present on admission. Hospitals are prohibited from billing the patient for these conditions where they are denied reimbursement. The goal is reduction of costs associated with HAI and thereby providing a dollar incentive for healthcare institutions to improve quality and safety. The HAI among these selected conditions are those which have some evidence base from centres having adopted practices or systems which demonstrably reduced infection, namely selected SSI, vascular-catheter associated infections and catheter-associated urinary tract infections. The cost of this policy of financial penalisation is as yet unknown, and the true impact on behaviour within US healthcare institutions remains to be seen and studied (Brown et al. 2009). One author (Carlet et al. 2009) argues that aiming for zero infections is unrealistic as while rates of HAI may fall with improved practice, it is not clear that the decrease will continue its trajectory to zero, or instead reach a lower limit which is non-zero. Our limited understanding of the pathophysiology of HAI also contributes to a reluctance to aim for zero, as despite apparently similar care, one patient develops an HAI while another avoids this outcome. The concept may be better expressed as zero tolerance of poor practice, amid a culture of investigating in blame free settings any such adverse outcomes in order to better prevent future similar outcomes.

In the UK too, the prospect of avoiding all preventable infections has captured the imagination of patient advocacy campaigns, and HAI prevention occupies a central place in the patient safety agenda (N.P.S.A. 2010). Withholding of reimbursement for acute Trusts in England now applies where that Trust failed to take preventive action in the case of a patient acquiring an HAI. An example might be failure to detect MRSA colonisation by admission screening in a patient who later develops invasive MRSA infection. No longer will HAI have impact only on clinical outcomes, and institutional reputation, but they will also have an additional financial consequence, beyond the known added cost of managing the greater length of stay, repeat surgery, prolonged antibiotic and other in-patient medical treatment.

HAI in UK

In the UK, the Department of Health (DH) acknowledges that there is no national surveillance system for the most common HAI, namely UTI. Indeed there are separate public health agencies within the UK dealing with each of the devolved regions. Instead of a national surveillance system a voluntary surveillance system for invasive infections permits insight into trends in these infections. The only robust data in England and Wales relate to MRSA BSI in acute Trusts via a system of mandatory reporting, and recent dramatic improvements in rates have been recorded, with the DH target of 50% reduction having been achieved by acute NHS Trusts in England and Wales in advance of the allotted time frame (Health Protection Agency U.K. 2010). There is however no assessment of how this relates to other deep-seated MRSA infections, or indeed to colonisation rates. At least one author suggests that MRSA infections in the broader sense rather than only BSI would be a more useful indicator of changes of rate of infection in either direction (Walker et al. 2008), which may be an increasingly relevant consideration as focussed efforts at achieving DH targets continue to drive down invasive infections. In this method, all MRSA isolated from sites other than screening samples would be recorded and reported, and could be a more sensitive indicator or early alert mechanism for an acute Trust that MRSA control measures were failing or succeeding.

C. difficile too is closely scrutinised in the UK, and is mandatorily reportable in England and Wales. The surveillance definition requires reporting of all laboratory positive tests. However there is no consensus on which *C. difficile* testing should be used. Thus, acute Trusts are at liberty to choose between toxin-based ELISA testing, GDH antigen and PCR-based testing, or combinations of these methods. Thus, although all Trusts test for *C. difficile* and report, there is no standard approach, a situation which renders comparison between acute Trusts, even between those of similar patient case-mix, meaningless. A consequence of this is the adverse incentive that choice of test influences the reported Trust *C. difficile* rate, which in turn influences the annual target *C. difficile* rate established as a performance indicator with the commissioners of healthcare. As a result, the nationally reported data are not comparable in the same way as MRSA BSI data. The only purpose that this system can serve therefore is for local monitoring and action within a Trust to determine whether control of *C. difficile* is effective. This problem does not solely relate to this single organism, or single disease, but illustrates further the challenges in data interpretation in HAI.

The focus on these high-profile infections in the UK is not because they are the commonest infections. Indeed repeated prevalence studies, most recently the HIS study in 2006 identify UTI as among the most commonly occurring infections associated with hospital care. There is no mandated system for recording or reporting these infections, although recent political developments have led to extension of mandatory reporting to include *E. coli* BSI, which may go some way towards addressing this deficit, as many will have urinary tract sources. Actions to reduce urinary-catheter associated UTI may well follow implementation of this system if this

is identified as a significant contributor to invasive infection rates. Transmission of other HAI such as glycopeptide-resistant enterococci, norovirus and drug-resistant Gram-negatives such as Acinetobacter or Pseudomonas species do not feature in these reporting systems, but each may have consequences for patients, including exposure to antimicrobial agents with toxicities to those of first line agents, or failure of first-line empiric treatment choice for hospital-acquired sepsis.

Obesity and HAI

Across developed nations, obesity has become a significant threat to public health (Karlsson and Beck 2010) with significant economic consequences for governmental and health budgets, and obese patients are being encountered by clinicians across diverse specialties, which may not yet have availed of the expertise of the bariatric surgery teams. Thus obese obstetric, cardiac surgery and vascular surgery patients will undergo Caesarean section, CABG and amputations, and may miss the multi-disciplinary input from the bariatric team dietician, endocrinologist, which may positively affect infection and other outcomes. These patients instead will challenge any surveillance system for SSI in particular, especially with their associated increased cardiovascular risk and likelihood of cardiac surgery (Rahmanian et al. 2007; Salehi Omran et al. 2007). These patients may also be at risk of other HAI including while in critical care, (Bochicchio et al. 2006) or undergoing gynaecological procedures (Chen et al. 2007) and systems of targeting surveillance on patient groups rather than on procedure types may need to be developed.

Travel and HAI and Antimicrobial Resistance

Compounding the global limitations of concerted surveillance efforts is the challenge posed by international travel for leisure or for ‘health tourism’. Patients exposed while abroad to organisms with different antimicrobial susceptibility to those in their home country, return colonised, and if later require hospitalisation, pose a transmission risk to other patients, or may suffer sepsis which will not respond to the local first-line empiric antibiotic choice. This was highlighted recently by the identification of *E. coli* and *Klebsiella* isolates with a common mechanism of carbapenemase resistance, namely NDM-1 (Kumarasamy et al. 2010). Antimicrobial stewardship is a key component of HAI management and there is an expectation that dissemination of drug-resistant organisms via global travel and healthcare contact will significantly affect the interaction between HAI and antimicrobial resistance. Coordinated international surveillance for these organisms with signature antibiograms could result in timely alerts of infection specialists that usual measures in sepsis management may not be effective in these patients.

Challenge of the Patient as Consumer

As healthcare systems increasingly adapt to better deliver more patient-centred care, with near-patient care models, home administration of intravenous antibiotics, local primary care delivering increasing services and the patient increasingly represented as informed consumer of care, the public reporting of HAI is purported to take on the function of informing a patient about the centre in which she will choose to access her care. Little is known however about the patient's decision-making process regarding healthcare, or whether a patient will indeed examine publicly available data, but public reporting of hospital cleanliness, rates of MRSA BSI, rates of CDI, rates of MRSA screening, rates of compliance with other performance indicators may be examined by at least some patients. Those developing publicly available metrics need to understand the perceptions of the target audience, and the public will need an understanding of the caveats required to interpret these data, particularly those of tertiary referral centres, differences in case-mix, and choice of metric.

Conclusions

The HAI global burden is unknown, but there are significant international efforts under way to amend this deficit in our understanding of the scale of the problem. Where it has been measured, the greatest impact of HAI is on those least equipped and resourced to manage them. WHO global patient safety challenge has the elements needed to support limited resource countries to promote basic standards in water, waste, injection and transfusion safety, and to implement effective hand hygiene. Networks of international surveillance and support for transitional countries have shown that meaningful records can be gathered and used to target preventive interventions. The question is, although it could be done, if we suspect that the problem is on a large scale, would resources be best used to measure it, or to try to reduce it?

In the developed world, there are systems for measuring certain HAI, but no consensus of definitions globally. Within NHSN perhaps is the best example of a set of standard definitions gradually being extended across the continent, and Europe is making progress in the same direction, but not necessarily with the same definitions.

Therefore, comparisons are not always possible, and there is a need to move towards harmonisation of basic measurements of parameters with agreed definitions to permit real comparisons between centres, and between countries. Additional potential benefits would result as these data rather than political targets could drive interventions for prevention and have impact on quality of patient care, clinical outcome, resource utilisation, and priority setting for a research agenda. The influence of sanctions for centres which fail to prevent infections is not yet known, and perhaps should focus on developing positives incentives, resources for innovative solutions rather than financial penalties and loss of institutional reputation.

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The Antibiotic Paradox

Ian M. Gould

Abstract Antibiotics are one of the great medical advances of all time, but their success has brought advanced warnings of their demise due to over-use. The story of antibiotics is full of paradoxes, from over-reliance leading to poor infection control practice, to over-use leading to resistance and spread of new resistant clones. These clones don't necessarily just replace susceptible clones but might bring additional burden of infection, leading to a net increase in numbers of infections. This chapter will investigate the implications of this for the control of healthcare acquired infection, with several examples of common hospital pathogens, showing not only increased prevelance but also virulence in some cases.

Keywords Resistance • HAI • Toxins • Virulence • MRSA • ESBL

Introduction

Antibiotics are arguably, the greatest discovery of the twentieth century but their very success has brought huge problems, which might be described as paradoxes. Firstly, this success has brought huge overuse and consequent resistance. While 20 years ago many might have argued about the links between use and resistance, these are now generally accepted as direct and irrefutable. Secondly, introduction of novel antibiotics immediately leads to calls for restrictions on their use, in order to delay the onset of resistance. This disincentives Pharmaceutical companies from crucial (but expensive) research to discover new classes of antibiotics. Thirdly, for all their success in battling infection and becoming the backbone of modern medical practice, it is increasingly evident that antibiotics are actually increasing the number of infections, and maybe even their severity, certainly in hospitals and possibly also in the community. It is this third paradox that I will discuss in this chapter.

I. M. Gould (✉)
Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill,
AB25 2ZN Aberdeen, Scotland
e-mail: i.m.gould@abdn.ac.uk

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_2, © Springer Science+Business Media, LLC 2011

Infection Control

The era of evidence based infection control really gained ground in the late nineteenth century with the Golden era of Bacteriology although the epidemiological basis had been layed over the proceeding century, arguably starting with the work of Alexander Gordon in Aberdeen, who in 1795 published his thesis on the contagious nature of puerperal fever (Gould 2010). Certainly, by the time the era of antibiotics started, in the 1930s, hospital hygiene, aseptic practices, patient isolation and disinfection were firmly established as major parts of good hospital practice (Williams 2008).

Who would have expected that now, in 2010, we are suffering the highest recorded rates of Hospital Acquired Infection (HAI), within living memory, and possibly since the nineteenth century when major surgery could not advance because of the problem of post operative infections (Lister 1867). Accurate statistics are not available of course, but since surveillance became fashionable, deaths from HAI in the USA have increased approximately sevenfold, from around 13,000 in 1992 to around 100,000 today (http://www.idsociety.org/). Moreover, public perception of this problem is real (Washer et al. 2008), antibiotic resistance has never been a bigger problem, and many, if not the majority of HAIs are caused by antibiotic resistant bacteria.

What is causing this undoubted increase in HAI at a time when concern about it has never been higher and resources spent on it are second to none? Possibly it is because we forgot the lessons learnt in the past, relying on antibiotics instead. To quote the US surgeon general "we can close the book on infectious diseases and declare the war on pestilence won" (Spellberg 2008). Or is it because antibiotics are somehow causing infections and countering our best efforts at infection control? (IC) (Gould 2008) Maybe it is a bit of both. Certainly there is plenty of evidence of poor IC practice in hospitals, albeit outside the operating theatre (Gould 2009). But what is the evidence that antibiotics are actually increasing the number of infections and maybe even their severity and why might this be the case and what is the evidence we can reverse these trends with antibiotic stewardship?

Antibiotics Are Increasing the Number of Infections

The most obvious example where antibiotics are increasing the number of infections is antibiotic associated diarrhoea, and in particular *Clostridium difficile* infection (Karas et al. 2010). This organism is most usually associated with prior antibiotic therapy and has seen big increases in the past decade, often associated with epidemics of multi-resistant, hypertoxin-producing strains. In particular, acquired resistance to quinolones and macrolides/lincosamides and natural resistance to cephalosporins has helped this organism to succeed at a time when these antibiot-

ics are amongst the most commonly used classes in most hospitals. The relationship between resistance and disease is not as clear as that between total use and disease as co-amoxiclav, another very commonly used agent is also associated with *C. difficile* disease although the organism remains susceptible.

MRSA

MRSA is currently causing a worldwide epidemic of the most notable proportion, possibly the biggest since the 1918–1919 flu pandemic, although it is actually comprised of many different epidemics due to different strains. There are currently separate strains causing major community epidemics in humans in the USA (Gould 2006) and in pigs and pig farmers in Holland and Denmark (Voss et al. 2005). Their relationship to antibiotic use is also probable if not proven. It is quite clear, at least in hospitals, that MRSA is an additional burden of infection. MSSA rates have not declined so if a hospital records its MRSA rate as 50%, then this usually means a doubling in the number of serious staphylococcal infections (HAI Newsletter 2010). While much of the spread of MRSA can correctly be attributed to poor IC practices, the influence of antibiotic use is now clear, not only in the selection and maintenance of such strains, but also in their spread, making IC all the more difficult (Monnet et al. 2004).

Numerous studies now document strong associations between prior antibiotic use and MRSA at an individual patient level and at an ecological level both in hospitals and communities. Simply put, if we did not use antibiotics, we would not have any problem with MRSA as it would have no survival advantage (Gould 2008).

What will happen with vancomycin resistance in *S. aureus*? We are seeing a slow but inexorable rise in low level resistance but there is little data yet to say that these strains will be an additional burden of infection, although they may already be showing more virulence and increased ability to cause chronic infection through tolerance, adherence and biofilm formation (Gould 2008).

Other Gram-positive Infections

The other Gram-positive organisms causing major problems in HAI are enterococci and coagulase negative staphylocci (CNS). It is no surprise that these organisms are mainly evident in multi resistant forms, enterococci often resistant to penicillins, macrolides and quinolones, always resistant to cephalosporins and increasingly glycopeptide and aminoglycoside resistant (http://www.rivm.nl/earss/). Similarly, CNS are methicillin resistant in the great majority of cases (http://www.eucast.org/). Fungi, in particular yeasts, should not be forgotten in this context either, broad spectrum antibiotic use being a well established predisposing factor. Antifungals too can select for different strains of emerging fungi.

Gram-negative Infections

Pseudomonas aeruginosa has long held a reputation as a common problem in hospitals, due to its innate antibiotic resistance. Other innately multi-drug resistant (MDR) organisms like *Burkholderia cepaciae* (Avgeri et al. 2009) and *Stenotrophomonas maltophilia* (Gabriel et al. 2004) are also causing increases in HAI rates usually associated with severe immunosuppression in individual patients. More convincingly perhaps, Acinetobacter is currently epidemic in many hospitals around the world and it is no coincidence that these epidemic strains are multi resistant, commonly including carbapenem resistance and sometimes Pan-resistance. Indeed, Acinetobacter has been described as the "Gram-negative MRSA" and certainly seems to have a unique ability to acquire resistance determinants (Fournier et al. 2006).

Comparative genomics of MDR *A. baumannii* French epidemic strain AYE show an 86-kb resistance island, the largest identified to date, with 45 resistance genes including 19 new putative resistant genes and a 20 kb genomic island "switch" flanked by transposases allowing acquisition of most of the genes recently acquired from *Pseudomonas*, *E.coli*, and *Salmonella.*

Arguably, the most significant development in Gram-negative resistance in the past 10 years has been the widespread transfer of mobile resistance elements determining cephalosporin, quinolone and/or carbapenem resistance in some of the most common human hospital pathogens, *E.coli*, *Klebsiella* spp. and other *Enterobacteriaceae* (Gould 2009; Kumarasumy et al. 2010). The spread of these resistances seems to have taken on an unanticipated importance such that talk of Pan-resistant bacteria is widespread and there are no anticipated new classes of agents in development in the foreseeable future. Other chapters in this book will address some of these bacteria in detail.

An important, and as yet unanswered question is whether these very worrying changes in susceptibility are associated with increases in the total number of infections, as discussed above, or whether as may commonly be assumed, they are merely replacing infections previously caused by susceptible strains. Unfortunately, we do not have robust surveillance systems in place to be able to answer these questions. Such surveillance systems usually collect only snapshots of organisms and describe the percentage resistance. Some such as EARSS (http://www.rivm.nl/earss/) and some National systems collect blood or invasive isolates and could calculate a denominator but these systems are usually voluntary so do not have a robust denominator. In any case, they also usually only report percentage resistance so it is difficult to abstract data on actual number of infections.

Looking at data from my own hospital laboratory, which serves a population of 500,000, we can obtain robust denominator data for bacteraemia and all clinical isolates, single episode per patient. Table 1 lists rates for 2008 as a percentage of 2001 levels (the earliest years data available). Any value over 100 is an increase. Only *S.maltophilia,* and *Citrobacter* show a decline while *E.coli*, *P.aeruginosa*, *Klebsiella*, *Enterobacter* and *Serratia* show at least a doubling. These latter species are amongst these demonstrating the greatest changes in resistance, during the past few years, in the Grampian region.

Table 1 Grampian. Unique clinical isolates per species 2008

Species	Specimen type	% of 2001 level
E.coli	bc	140
	all	400
P.aeruginosa	bc	150
	all	200
Klebsiella	bc	200
	all	200
S.maltophilis	bc	50
	all	100
B.cepaciiae	bc	100
	all	100
Acinetobacter	bc	100
	all	30
Enterobacter	bc	100
	all	200
Citrobacter	bc	100
	all	100
Serratia	bc	300
	all	200

bc blood culture
all all types of specimens

On studying EARSS data for the years 2001/2002 versus 2007 the only comparable data publicly available is for *E.coli*. In 2001/2003 20 countries reported 13,263 episodes of *E.coli* bacteriaemia. The reporting laboratories covered 240,000 beds and received 1.3 million blood cultures. Comparable data for 2007 were 30 countries (50% increase), 46,524 episodes of *E.coli* bacteraemia (3–4-fold increase), 350,000 beds (almost 50% increase), 2.8 million blood cultures (approximately twofold increase) (http://www.rivm.nl/earss/).

Unpublished data from the Scottish Voluntary National Surveillance of blood cultures, which seems to have had consistent methods of adherence to reporting between 2001 and 2008 (Camilla Wuffe personal communication) are seen in Figs. 1 and 2 and cover a population of just over 5 million and 27 reporting laboratories. While the data cannot be considered robust, it gives great cause for concern and requires much more robust surveillance to be performed in future. In particular, *E.coli* and *Klebsiella* bacteraemia doubled between 2001 and 2008. Similar data from England is shown on the HPA website (http://www.hpa.org.uk).

Antibiotics Are Increasing the Severity of Infections

When a new antibiotic resistance manifests, it is often claimed that the fitness cost to the organism is too great for the strain to be pathogenic (Levin 2001). Unfortunately, time and again this proves to be short lived optimism, as genetic adaption al-

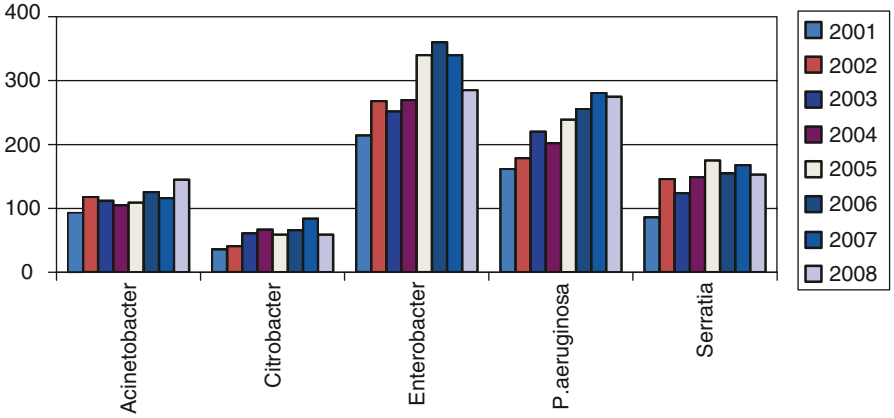
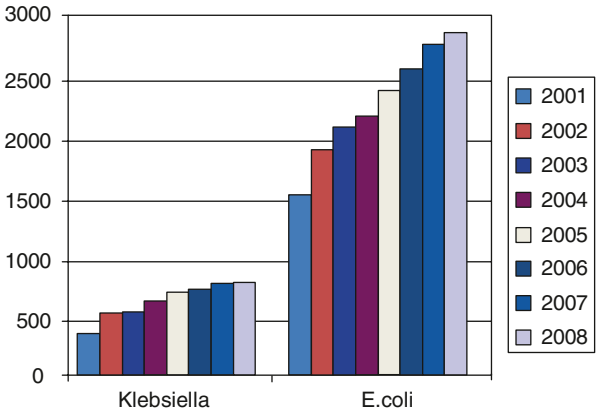


Fig. 1 Health Protection Scotland reported bacteraemia

Fig. 2 Health Protection Scotland reported bacteraemia



lows compensatory mutations. *Clostridium difficile*, MRSA, especially PVL strains and perhaps glycopeptide intermediate *S.aureus* are examples where virulence factors can be associated with resistance determinants, sometimes on pathogenicity islands (Lindsay and Holden 2004).

Moreover, the inability to deliver adequate empiric therapy is increased in resistance, more so where there is (linked) multi resistance, encoded for on integrons and other mobile genetic elements. Outcomes are poorer and mortality higher (Kumar et al. 2006). Worse still, alternative therapies may not be so efficacious, even if administered in a timely manner. Again the example of glycopeptides and MRSA springs to mind (Lodise et al. 2007). It is well established that the glycopeptides are sub-optimal therapy when compared with semi-synthetic penicillin for the treatment of methicillin susceptible *S.aureus* (MSSA). Two meta-analysis suggest mortality from MRSA infection is double that of equivalent MSSA infection (Whitby et al. 2001; Cosgrove et al. 2003). No wonder that mortality from HAI is increasing.

Why Is HAI Increasing in Frequency and Severity?

The easiest explanation for the data I have presented is that it is either false (the surveillance systems are not robust) or that the increasingly aged and immunosuppressed hospital population is more susceptible to infection. Possibly, we have not fully rediscovered good IC practice, having lost ground in the golden antibiotic era when we were lulled into a false sense of security, thinking that antibiotics had infection diseases beaten. I clearly remember one of my mentors in the 1980s telling me we had little need for isolation rooms in modern hospitals. There may be elements of truth to this, but I do not think it's the full explanation. If that were case, then why have HAIs due to susceptible organisms not shown an increase rather than just remained stable? Perhaps also, blood culture systems are better or more blood cultures are being submitted but this is not the case in our own laboratory [unpublished] and it is hard to credit that *E.coli* or *Klebsiella* are better isolated in new blood culture systems.

More plausibly antibiotics not only select for and maintain resistance, but they also can increase transmissibility, colonization and pathogenicity (Gould 2008). Increased transmissibility of antibiotic resistant organisms in patients on antibiotics has long been appreciated (Berntsen and McDermott 1960). More recently, carriers of MRSA in Hong Kong in 2008 were shown to have increased numbers of MRSA in their noses if they were receiving quinolones or cephalosporins, both of which the MRSA isolates were resistant to (Cheng et al. 2008). Simplistically, such antibiotics will ablate the normal (protective) bacterial flora, allowing colonisation and an overgrowth with resistant invaders such as MRSA (in the nose) or ESBL producing *E.coli* in the gut. Other possible mechanisms that may operate to increase colonization and pathogenicity and can be attributed to commonly used antibiotics are listed in Table 2 and a proposed biological model for the vicious cycle of exposure, colonization, infection and death is illustrated in Fig. 3. Not least, the simplistic notion that simple infections not responding to first line treatment, will develop into more serious, often invasive infections, should not be discounted.

Are we in danger of completely negating the antibiotic miracle in our overuse of antibiotics? In other words, are we seeing such a rise in resistant infection that it will ultimately completely counter the beneficial effects of antibiotics?

What Can We Do?

Clearly more is required than standard IC responses. In some isolated examples, dedicated and targeted IC can work e.g. on catheter care to reduce *MSSA* and MRSA bacteraemia and surveillance cultures for MRSA on admission to hospital as a guide to isolation and decolonisation strategies (Reilly et al. 2010). But these strategies can be expensive. Arguably they are akin to firefighting.

Table 2 Causes of increased transmission, adherence and pathogenicity of MRSA when exposed to antibiotics

- Biofilm formation
- Small colony variants
- Efflux
- Hypermutation
- Skin/RT colonization → transmissibility
- Fibrinonectin-binding protein
- Toxin production eg ∝, TSST-1
- SOS response → horizontal gene transfer
- Phage induction
- Quorum sensing
- Agr expression
- Autolysis
- Intracellular persistence

RT respiratory tract
TSST Toxic shock syndrome toxin
Agr Accessory gene regulation

What is required is tackling of the problem at its root cause, namely the gross over use of antibiotics. The Cochrane review on prescribing interventions to control resistance in hospitals was very limited in the robust evidence it found (Davey et al. 2005) but there has been a significant increase in the number of good quality studies published since 2002. There is now reasonable evidence that rates of MRSA, *C.difficile*, VRE and multi resistant Gram-negatives can be reversed by modulating use of key agents such as cephalosporins and quinolones, not withstanding the particular problems posed by integrons carrying multiple resistant determinants (Gould 2008; Davey et al. 2005).

The real problem for the future, of course, is how to do this without "squeezing the balloon", transferring the resistance selection pressure to other classes of agents. This highlights another paradox, that of current antibiotic policies which tend to lead to a lack of diversity of use of different classes of antibiotics. Diversity of use is probably one of the best strategies to delay emergence of resistance, although a lack of choice of truly different drug classes makes its implementation problematic. Moreover, the holy grail, and the most difficult thing is to achieve total reduction in prescribing while not compromising patient outcomes. Again, this isn't something current strategies are good at achieving. This takes us full circle to Volume 1 of this series and the methods of stewardship. In the absence of a good pipeline of new drugs, it is the balance between the individual patient and society as a whole, otherwise known as the ecological perspective, that has to be clearly established and debated. We need to get clever, quickly. Some examples might include only using surgical prophylaxis when it is clearly established to lead to an overall reduction in antibiotic use. This, of course, will mean accepting the occurrence of a certain number of potentially avoidable infections. The potential severity of the infection will also

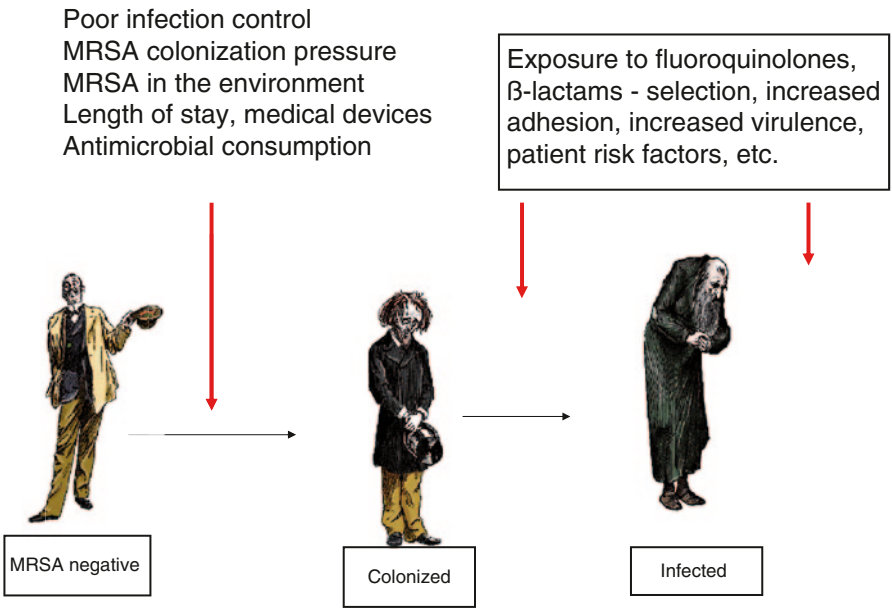


Fig. 3 A reasonable biological model? (Adapted from Monnet 2006)

have to be taken into consideration. A graft infection is very different from a superficial wound infection. Similar difficult, long term, decisions will have to be taken in other areas e.g. primary care and the prophylaxis strategies used for highly immunosuppressed patients. Quinolone prophylaxis in haematological malignancy is a good example, with lives saved, but an uncertain future due to resistance.

In conclusion, there are many difficult decisions to be made. The medical profession is certainly more receptive to the problems since the advent of MRSA and the current crop of virulent strains of *C.difficile,* but much more debate and education has to follow to change attitudes and beliefs in order that real changes in prescribing practice can be instituted and maintained. And it isn't just the medical profession that is responsible or needs to lead on this. Society, at all levels in all countries of the world needs to act on the problems of antibiotic use and abuse. Otherwise, current trends of increasing antibiotic use worldwide will only get worse, and with them the current problems of antibiotic resistance and HAI will only seem like the beginning.

Essentially we need new strategies for disease prevention less reliant on antibiotics. Vaccines are the obvious area to expand. By their nature, antibiotics are only a short term strategy, particularly if overused in the current fashion. They are truly a victim of their own success.

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The Epidemiology of Pan/Extreme Drug Resistance

Yoshiro Hayashi and David L. Paterson

Abstract Multidrug resistance in Gram-negative bacilli is clearly of global concern. The purpose of this chapter is to review the epidemiology of organisms referred to as pan-resistant (PDR) or exhibiting extreme drug resistance (also referred to as extensive drug resistance—XDR). In order to better understand the epidemiology, it is first essential to define what is regarded as PDR or XDR.

Keywords Antibiotic resistance • Carbapenemases • Colistin • Tigecycline • Antibiotic combinations • PDR

Terminology and Definitions Regarding Antibiotic Resistance in Gram-negative Bacilli

Terminology and definitions regarding antibiotic resistance in Gram-negative bacilli (GNB) has been chaotic, unlike the situation in *Mycobacterium tuberculosis*. Until recently, there has been no agreement on the definitions even for "multi-drug resistance" (MDR) in typical problematic GNBs such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; resistance to at least two, three, four, or eight of antibiotics variably used as a definition depending on individual investigators. Additionally, a number of terms such as "extreme-drug resistant", "extensive-drug resistant", "extensively-drug resistant" and "extremely-drug resistant", have been abbreviated as XDR. The lack of harmonized definitions for MDR, XDR, and PDR has made it difficult to consistently collect or compare epidemiological surveillance data among hospitals and countries, and to utilize them for public health purposes.

Paterson proposed a definition of MDR and pan-drug resistant (PDR) in GNBs in 2006. In his proposal, MDR is defined as diminished susceptibility to more than one of the following five drug classes; anti-pseudomonal cephalosporins, anti-pseudomonal carbapenems, β-lactam plus β-lactamase inhibitor combinations,

Y. Hayashi (✉)
The University of Queensland, UQ Centre for Clinical Research, Herston, Brisbane, Australia
e-mail: y.hayashi@uq.edu.au

Royal Brisbane and Women's Hospital, Department of Intensive Care Medicine, Herston, Brisbane, Australia

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_3, © Springer Science+Business Media, LLC 2011

anti-pseudomonal fluoroquinolones, and aminoglycosides, and PDR is defined as diminished susceptibility to all of the antibiotics recommended for the empirical treatment of ventilator-associated pneumonia; namely, cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin. Subsequently, in a 2007 editorial by Paterson and Doi, GNBs resistant to all available antibiotics were defined as having an "extreme-drug resistant" (XDR) phenotype. In other words, XDR was used to define isolates lacking susceptibility to all of the β-lactam and quinolone antibiotics included in Paterson's definition of PDR, plus ticarcillin-clavulanate, ampicillin-sulbactam, all aminoglycosides, tigecycline, and polymyxins (colistin and polymyxin B). These definitions were proposed in order to be practical and relevant to clinical practice so that they could be easily introduced in hospitals worldwide.

However, the proposed definitions by Paterson had several deficits. A representative criticism was made by Falagas and summarised as follows. First, the prefix "pan-" has a meaning in Greek (and in medicine) of "all". Therefore, PDR cannot be interpreted in a sense other than signifying resistance to all antibiotics. However, in Paterson's definition, PDR-GNBs are less resistant to XDR-GNBs and PDR-GNBs are not resistant to all antibiotics. Second, the term "extreme-drug resistant" (XDR) has already been an established term in the field of oncology with a meaning of significantly decreased responsiveness of tumor-cell colonies *in vitro* to a studied chemotherapeutic agent, whereas "extensively-drug resistant" (XDR) has also been used for XDR *M. tuberculosis*, which is defined as *M. tuberculosis* resistant to first-line agents (i.e. isoniazid and rifampicin), to a fluoroquinolone, and at least one of the three second-line parenteral agents. Third, Paterson's definitions produce a category of highly drug resistant GNBs which do not meet his criteria of PDR and XDR. Therefore, Falagas proposed to use the terms MDR, extensive-drug resistant (XDR), and PDR, with a meaning of "resistant to more than two classes of antibiotics", "resistant to all but one or two classes of antibiotics", and "resistant to all classes of antibiotics", respectively.

Thereafter, authorities including Falagas, Paterson, and representatives of the European Centre for Diseases Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) have undertaken generation of harmonized terms and definitions regarding the degree of multiple antibiotic resistance. In their proposal of 2010, three different lists of antimicrobial categories for GNBs—namely for Enterobacteriaceae, *P. aeruginosa*, or *Acinetobacter* spp.—are designed to define MDR-, XDR-, and PDR-GNBs (Tables 1–3). As a general rule, MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug-resistant (XDR) is defined as non-susceptibility in all antimicrobial categories with the exception of one or two antimicrobial categories. PDR is defined as non-susceptibility to all agents in all antimicrobial categories.

These definitions for MDR, XDR, and PDR are much more rigorous than any other previous definitions. However, despite the rigor for the number of resistant antimicrobial agents and antimicrobial categories, definitions for non-susceptibility in the expert proposal are still loose; non-susceptibility is defined as intermediate or resistant to an antimicrobial agent according to CLSI or EUCAST criteria. Unfortunately CLSI and EUCAST criteria are not harmonised. This means, for example,

Table 1 Non-susceptibility rates of *Klebsiella* spp. or *K. pneumoniae* to carbapenems and representative antibiotics in surveillance studies

Area	Microorganisms	Year	N	IPM (%)	MER (%)	CIP (%)	LEV (%)	AMK (%)	GEN (%)	Ref.
Global	*K.* pneumoniae	2004–2007	10,644	0.7	4.6	–	17.0	4.5	–	Garrison et al. 2009
		2005–2007	2,604	1.6		22.4		6.9		Hawser et al. 2009
	K. pneumonia ESBL+	2004–2007	1,495	2.7	13.9	–	64.1	18.8	–	Garrison et al. 2009
		2005–2007	683	4.7		65.1		24.6		Hawser et al. 2009
Europe	*K. pneumoniae*	2004–2007	2,331	–	1.7[a]	–	14.3	3.1	–	Norskov-Lauritsen et al. 2009
	K. pneumonia ESBL+	2004–2007	316	–	0.7[a]	–	53.5	11.4	–	Norskov-Lauritsen et al. 2009
Greece (ICU)	*K. pneumoniae*	2009	384	76.0	66.7	85.1	–	57.6	26.3	WHONET Greece
Asia-Pacific	*Klebsiella* spp.	2008	444	4.5		–	21.2	–	22.3	Farrell et al. 2010
	Klebsiella spp. ESBL+	2008	160	1.2		–	46.9	–	53.7	Farrell et al. 2010
China	*Klebsiella* spp.	2003–2008	548	1.5	1.7	42.1	–	19.3	–	Wang et al. 2010
India	*K. pneumoniae*	2008	90	6.7		54.4		17.8		Hsueh et al. 2010
	K. pneumonia ESBL+	2008	49	12.2		91.8		32.6		Hsueh et al. 2010
Latin America	*Klebsiella* spp.	2005–2006	915	2.1	2.5	37.3	–	26.6	34.0	Bantar et al. 2009
North America	*K. pneumoniae*	2004–2006	3,289	0.4	–	–	10.6	1.5	–	Reinert et al. 2007
United States	*K. pneumoniae*	2007	931	0.0	2.0	–	5.9	1.7	–	Dowzicky and Park 2008
	K. pneumonia ESBL+	2007	78	–	31.2	–	76.9	26.9	–	Dowzicky and Park 2008
	Klebsiella spp.	2007	317	9.1	8.5	21.8	21.1	–	10.4	Jones et al. 2008
Canada	*K. pneumoniae*	2005–2006	224	–	0.0	4.9	4.4	0.4	2.3	Dowzicky and Park 2008

N number of isolates; *IPM* imipenem; *MER* meropenem; *CIP* ciprofloxacin; *LEV* levofloxacin; *AMK* amikacin; *GEN* gentamicin

Table 2 Non-susceptibility rates of *P. aeruginosa* to carbapenems and representative antibiotics in surveillance studies

Area	Year	N	IPM (%)	MER (%)	TZP (%)	CFP (%)	CIP (%)	LEV (%)	AMK (%)	GEN (%)	PMB (%)	COL (%)	Ref.
Global	2004–2007	10,825	17.4	20.4	12.3	24.4	–	36.5	7.3	–	–		Garrison et al. 2009
	2005–2007	1,746	25.2		13.5	22.3	27.3		13.5		–		Hawser et al. 2009
Europe	2004–2007	2,653	–	20.6	13.2	11.2	–	33.8	7.2	–	–	–	Norskov-Lauritsen et al. 2009
Greece (ICU)	2009	238	51.8	–	35.0	54.1	–	–	41.2	47.8	–	–	WHONET
Asia/Pacific	2008	426	22.8		20.4	24.6	–	25.8	–	14.3	0.2		Farrell et al. 2010
China	2003–2008	548	28.5	19.5	26.3	33.0	32.1	–	21.2	–	–	–	Wang et al. 2010
Japan	2007	673	29.2	15.3	6.1	–	17.1	20.8	2.7	8.8	–	–	Yamaguchi et al. 2009
India	2008	29	17.2		17.2	41.4	58.6		37.9		–		Hsueh et al. 2010
Taiwan	2005	164	10	10	18	21	19	23	6	23	–	9.0	Jean et al. 2009
Latin America	2004–2006	254	34.0	–	13.8	42.1	–	54.7	28.0	–	–	–	Reinert et al. 2007
North America	2004–2006	3,344	15.4	–	9.6	21.8	–	36.7	2.8	–	–	–	Reinert et al. 2007
United States	2007	1,054	14.0	16.2	9.8	22.3	–	34.7	4.1	–	–	–	Dowzicky and Park 2008
	2007	454	22.5	16.7	11.0	14.3	25.6	28.4	–	13.2	–	–	Jones et al. 2008
Canada	2005–2006	419	–	18.8	9.1	21.5	29.6	32.0	3.8	32.0	–	–	Dowzicky and Park 2008

N number of isolates; *IPM* imipenem; *MER* meropenem; *TZP* piperacillin/tazobactam; *CFP* cefepime; *CIP* ciprofloxacin; *LEV* levofloxacin; *AMK* amikacin; *GEN* gentamicin; *PMB* polymyxin B; *COL* colistin

Table 3 Non-susceptibility rates of *A. baumanii* to carbapenems and representative antibiotics in surveillance studies

Area	Year	N	IPM (%)	MER (%)	CIP (%)	LEV (%)	AMK (%)	GEN (%)	PMB (%)	COL (%)	TIG*	Ref.
Global	2004–2007	6,292	17.7	41.0		53.9	30.4	–	–		0.5/1	Garrison et al. 2009
	2004–2008	1,591		32.0[a]		43.8	29.2		–		0.25/1	Wang and Dowzicky 2010
Global (ICU)	2004–2008	489		50.4[a]		65.8	48.5		–		0.5/2	Wang and Dowzicky 2010
Asia/Pacific	2004–2008	246		41.2[a]		40.2	39.4		–		0.25/2	Wang and Dowzicky 2010
	2008	397	51.4	–		68.0	–	71.3	0.0		0.5/2	Farrell et al. 2010
China	2003–2008	486	22.8	24.7	59.6	–	51.5	–	–	–	–	Wang et al. 2010
Japan	2007	598	3.7	–	11.7	7.5	–	–	–	–	–	Yamaguchi et al. 2009
India	2008	11	81.9	–	90.9	81.8	90.9	–	–	–	–	Hawser et al. 2010
Taiwan	2005	167	25.0	28.0		67.0	63.0	72.0	–	6.0	2/4	Jean et al. 2009
Europe	2004–2008	423		30.0[a]		39.5	29.1		–		0.25/1	Wang and Dowzicky 2010
	2004–2007	1,560	–	31.5[b]		45.0	28.6	–	–	–	0.25/1	Norskov-Lauritsen et al. 2009
Greece (ICU)	2009	288	89.3	79.9	98.9	–	82.7	71.5	–	–	–	WHONET
Latin America	2004–2008	150		53.7[a]		72.7	64.7		–		0.5/2	Wang and Dowzicky 2010
	2005–2006	735	52.2	53.2	84.0	–	72.2	67.0	–	–	–	Bantar et al. 2009
Middle East	2004–2008	46		44.4[a]		82.6	60.9				1/4	Wang and Dowzicky 2010
North America	2004–2008	717		21.3[a]		39.1	16.3				0.25/1	Wang and Dowzicky 2010
United States	2007	486	9.4	36.1	–	57.8	28.4	–	–	–	–	Dowzicky and Park 2008
	2007	133	43.6	46.6	61.7	60.9	–	52.6	–	–	–	Jones et al. 2008
Canada	2005–2006	28	–	0.0	10.7	0.0	7.1	10.7	–	–	0.5/2	Dowzicky and Park 2008

*MIC50/MIC90 (mg/mL)

[a] 2006–2008, No of tested isolates is less than N

[b] 2006–2007, No of tested isolates is less than N

N number of isolates; *IPM* imipenem; *MER* meropenem; *CIP* ciprofloxacin; *LEV* levofloxacin; *AMK* amikacin; *GEN* gentamicin; *PMB* polymyxin B; *COL* colistin; *TIG* tigecycline

a strain of *P. aeruginosa* with a MIC of 32 or 64 mg/L for piperacillin-tazobactam, which is interpreted non-susceptible according to EUCAST but susceptible according to CLSI, could be categorised differently depending on the country in which antimicrobial susceptibility testing is performed.

Clearly, no perfect definition can be established. The joint ECDC and CDC definitions required 3 years for consensus to be reached, and therefore should be regarded as the current standard to be used worldwide.

Reported Cases of GNBs for Which There is no Commercially Available Drug

Previous reports of PDR GNBs are based on variable definitions made by different investigators, not the standard ECDC/CDC definition. In this section, reported clinical cases of GNBs for which there seems to be no commercially available drug for treatment, are to be reviewed. Most of the cases of XDR/PDR GNBs have occurred following considerable prescription of polymyxins (and tigecycline) due to an increased recovery rate of carbapenem-resistant GNBs.

Pseudomonas aeruginosa

In New York, where polymyxins were re-introduced in the early 2000s due to the high prevalence of carbapenem-resistant GNBs, resistance to polymyxin B in *P. aeruginosa* has emerged. Active surveillance in 2003 to determine the prevalence of *P. aeruginosa* isolates with reduced susceptibility to polymyxin B, showed that, of 523 isolates from 11 hospitals in New York, 25 (5%) were non-susceptible to polymyxin B (MICs 4–8 mg/L), although this study did not show the degree of multiple resistance.

In a Greek ICU, five cases of ventilator-associated pneumonia due to an identical genotype of $bla_{\text{VIM-1}}$ positive *P. aeruginosa* resistant to all tested antibiotics including colistin occurred after prolonged use of carbapenem and colistin in 2005.

In Taiwan, VIM-3 metallo-β-lactamase has been the predominant cause of carbapenem-resistance in *P. aeruginosa*. Of 308 carbapenem non-susceptible *P. aeruginosa* isolates, which were collected from 2000 to 2005 in Taiwan, 27 (9%) were resistant to all tested antibiotics except colistin and three isolates (1%) were resistant to all tested antibiotics with intermediate-resistance to colistin (MIC 4 mg/L) (Tseng et al. 2009).

In Japan, where IMP-metallo-β-lactamese has been predominantly found in carbapenem-resistant *P. aeruginosa* isolates, MICs of polymyxin B and colistin obtained from 75 clinical isolates of *P. aeruginosa* harbouring the bla_{IMP}-type gene (94.7% of them were resistant to all of imipenem, ciprofloxacin and tobramycin) recovered in a single centre in Japan were relatively high: MIC_{50} (mg/L)/MIC_{90} (mg/L) of polymyxin B and colistin were 4/4 and 8/16, respectively, although no injectable polymyxins have been available in the country for several decades.

A clinical case of sepsis due to *P. aeruginosa* resistant to all tested antibiotics with intermediate resistance to amikacin (MIC 16 mg/L) was reported from Belgium (Poirel et al. 2010).

Acinetobacter baumannii

Carbapenems are generally the most potent antibiotics for treating *A. baumannii*. However, carbapenem-resistance in *A. baumannii*, which is mediated predominantly by class D OXA-type enzymes (e.g. OXA-23, OXA-40, OXA-58) with or without the loss of outer membrane proteins and/or the up-regulation of efflux pumps, has been reported in most parts of the world. For treating carbapenem-resistant *A. baumannii*, in general, colistin, polymyxin B, and tigecycline are considered as the last-resort antibiotics. However, *A. baumannii* isolates resistant to polymyxins and/or tigecycline in addition to carbapenems are emerging. Modification of lipopolysaccharides and the over-expression of the AdeABC efflux pump are thought to be associated to resistance to polymyxins and tigecycline, respectively.

According to a report from a South Korean ICU, of 63 isolates of *Acinetobacter* spp. (44 *A. baumannii*), 31.7% and 34.9% were resistant to imipenem and meropenem, respectively, and 27.0% and 30.2% were resistant to polymyxin B and colistin, respectively (Park et al. 2009). Eight isolates were resistant to all tested antibiotics including polymyxin B, colistin, and tigecycline (MICs 4 mg/L). Six of the eight isolates caused infections and the crude 30-day mortality rate was 66.7%.

In the United States, *A. baumannii* that lacked susceptibility to all commercially available antibiotics including colistin (MIC > 1024 mg/L) and tigecycline (MIC 2 mg/L) was recovered from a 55 year-old post-lung transplantation patient (Doi et al. 2009).

In Portugal, *A. baumannii* resistant to all tested antibiotics including colistin (MIC 32 mg/L) and tigecycline (MIC 16–32 mg/L) were recovered from a 37-year-old patient with acute pancreatitis (Grosso et al. 2010).

In Greece *A. baumannii* isolates resistant to all anti-pseudomonal agents including colistin and sulbactam were also recovered although susceptibility testing was not performed for tigecycline (Falagas et al. 2008).

Klebsiella pneumoniae

Following frequent use of carbapenems for treating ESBL-producing *K. pneumoniae*, carbapenem-resistance in *K. pneumoniae* has become a significant issue worldwide. The production of carbapenemases is the predominant cause of carbapenem-resistance in *K. pneumoniae*. A class B metallo-β-lactamases, VIM-1, and a class A serine β-lactamase, KPC, have been regarded as major responsible enzymes in *K. pneumoniae* for hydrolysing carbepenems. A novel class B metallo-

β-lactamase, NDM-1, is now being recognised as another important carbapenemase in *K. pneumoniae*. VIM-1, KPC-, and NDM-1-producing *K. pneumoniae* were isolated predominantly in Greece, the United States and India, respectively. As might be expected, XDR/PDR *K. pneumoniae* has already been emerging possibly due to increasing prescription of polymyxins and tigecycline.

Colistin-resistant *K. pneumoniae* were isolated in a Greek ICU in 2004, where empirical colistin was frequently used for the coverage of carbapenem-resistant GNRs (Antoniadou et al. 2007). Those strains are frequently ESBL and/or MBL producers as well. Five strains were associated with infections (VAP, blood stream infection and soft tissue infection) in four patients. Three of the five strains were susceptible only to tetracyclines. Crude mortality of those patients was 100%. Development of polymyxin B resistance during treatment with polymyxin B for KPC-producing *K. pneumoniae,* which were initially susceptible to polymyxin B is also documented. In a report from New York, in three patients out of 16 patients treated with polymyxin B (+/− tigecycline) for KPC-producing *K. pneumoniae*, dramatic increases in MICs for polymyxin B (from 0.75–1.5 μg/mL to 12–1024 μg/mL) were observed during treatment with polymyxin B (duration of polymyxin B: 5–21 days) (Lee et al. 2009). According to in vitro susceptibility testing results of 30 colistin-resistant GNRs from a Greek university hospital, 14 strains out of 22 colistin-resistant *K. pneumoniae* were resistant to both colistin and imipenem (Samonis et al. 2010). Twelve strains out of the 14 were only susceptible to nonstandard antibiotics such as tetracycline and/or fosfomycin and/or chloramphenicol, and one strain out of the 14 was resistant to all tested antibiotics. In Hungary eight strains out of nine KPC-producing *K. pneumoniae* recovered were resistant to colistin (Tóth et al. 2010). All of the nine strains were non-susceptible to almost all antibiotics including tetracycline and tigecycline but, remarkably, eight of the nine strains were susceptible to trimethoprim/sulfamethoxazole.

In New York, two PDR isolates of *K. pneumoniae* were isolated in 2007 and 2008 (Elemam et al. 2009). Both isolates were KPC-producers and resistant to all tested antibiotics including polymyxin B (MIC 4 mg/L and ≥8 mg/L) and tigecycline (MIC ≥8 mg/L). These were recovered from patients who had a recent history of treatment with both polymyxin B and tigecycline for KPC-producing *K. pneumoniae*.

One isolate of NDM-1 producing *K. pneumoniae* in India was resistant to all tested antibiotics including colistin (MIC >32 mg/L) and tigecycline (MIC 8 mg/L) (Kumarasamy et al. 2010).

Global Epidemiology

The situation where there is no drug of choice for treating GNBs is still very rare. However, as shown above, several clinical cases of PDR in *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* have already been reported. As discussed in the following section, carbapenem-resistance in those three GNBs is already prevalent in nearly all parts of the world. This means that an outbreak of XDR or PDR GNBs is ready

to occur anywhere. In addition, accumulated clinical experience with tigecycline for treating serious infections due to GNBs has not been positive—tigecycline treated patients have had higher mortality rates that patients treated with comparators. Strictly speaking, fosfomycin, minocycline, and chloramphenicol occasionally may retain low MICs for the GNBs resistant to all standard antibiotics and polymyxins. However, clinical efficacy of those antibiotics in moderate to serious cases largely remains unstudied.

Resistance in GNBs Seen in Global Surveillance Studies

There have been several global and nationwide surveillance activities to monitor antimicrobial susceptibilities. Unfortunately, through these published documents, very limited information is obtainable regarding XDR/PDR because susceptibilities to polymyxins have been rarely tested in those surveillance activities and information about degree of multiple resistances are generally lacking. However, those data have shown that issue of non-susceptibility to carbapebems in GNBs, which is the precursor to XDR/PDR, has already became common in *A. baumannii* and *P. aeruginosa* and is emerging in Enterobacteriaceae, especially in *K. pneumoniae*, in nearly all parts of the world. The following description is focused on carbapenem-resistance rate by region which recent surveillance studies show.

Europe

Rates of carbapenem-nonsusceptibility in *A. baumannii*, *P. aeruginosa* and *K. pneumonia* in Europe since 2004 are 30.0–31.5, 20.6% and 1.7%, respectively. Greece has been experiencing extremely high resistance rates in *A. baumannii*. The Greek System for Surveillance of Antimicrobial Resistance (GSSAR) shows that the carbapenem-nonsusceptible rate in *A. baumannii* isolates obtained in 2009 was 89.3% for imipenem and 79.9% for meropenem. Carbpenem-nonsusceptibility rates in *P. aeruginosa* and *K. pneumoniae* in Greece are also critically high; 51.8% and 76.0%, respectively, in ICUs in 2009.

Surveillance data which were obtained in the early 2000s also demonstrated that carbapenem-non-susceptibile rates in *A. baumannii* in Spain and Turkey were 47.8 and 48.0%, respectively (Picazo et al. 2006; Korten et al. 2007). However, recent data in those countries about carbapenem-nonsusceptibility in *A. baumannii* are not available. European Antimicrobial Resistance Surveillance (EARSS) data show that the carbapenem-nonsusceptible rate in *P. aeruginosa* in 2007 in Turkey was 31.0%. EARSS data also show that carbapenem-nonsusceptible rates in *P. aeruginosa* in Germany and Italy were 31.5 and 32.1% in 2007, respectively, and the carbapenem-nonsusceptible rate in *K. pneumoniae* in Israel was 21.9% in 2007. This high carbapenem-nonsusceptible rate of *K. pneumoniae* in Israel is consistent with the many reports of isolation of KPC-producing *K. pneumoniae* from that country.

Asia

Rates of carbapenem resistance in Asian hospitals are amongst the highest in the world. Carbapenem susceptibility in *A. baumannii* deteriorated from 90% in 2002 to just 50% in 2007. In many ICUs across Asia, carbapenem resistant *A. baumannii* is now endemic. Carbapenem resistant, *P. aeruginosa* is also highly prevalent. The recent onset of NDM-1 producing carbapenem resistant *K. pneumoniae* in India and Pakistan has become a major threat to the region. In some Indian hospitals, 50% of *K. pneumoniae* isolates are carbapenem resistant. NDM-1 producing *K. pneumoniae* has been found in Bangladesh, Singapore, Taiwan, Japan and Australia. In retrospect, the first NDM-1 producers were found in India in strains from 2006.

South America

Carbapenem-nonsusceptible rates in *A. baumannii*, *P. aeruginosa* and *Klebsiella* spp. in Latin America since 2004 are 53.7, 34.0 and 2.1–2.5%, respectively. All these nonsusceptible rates are higher than Europe, Asia-Pacific region, and North America. Unfortunately more specific information in Latin America is relatively limited.

North America

Carbapenem-nonsusceptible rates in *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* in North America since 2004 are 21.3, 15.4 and 0.4%, respectively. The United States has been experiencing more serious antibiotic resistance issue in GNBs than Canada. Carbapenem resistance in *K. pneumoniae* due to the KPC beta-lactamase is a major problem in New York City. KPC producers have now been found throughout the United States.

Concluding Remarks

The epidemiology of MDR GNBs shows major hotspots for carbapenem resistance in the Northeast of the United States, Latin America, Greece, Israel and throughout Asia. The use of polymyxins and tigecycline to treat carbapenem resistant organisms has led to the disastrous situation where PDR strains are now present. No commercially available options are in use for these strains. We can only hope that infection control and antibiotic stewardship interventions can control the spread of PDR strains before they become widespread in hospitals. Of even greater concern is the potential for community-acquired XDR or PDR *E. coli* infections. This is clearly of major public health importance.

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Hospital Antibiotic Stewardship to Control Resistance—How Should It be Done?

Ian M. Gould

Abstract Antibiotic stewardship was originally developed as a cost saving initiative. Increasingly it is looked to as a mechanism of slowing the tide of resistance. There is an accumulating body of robust publications which show it is possible to reduce resistance rates across a wide spectrum of organisms by reducing broad spectrum antibiotic use, in particular cephalosporins and quinolones. The resistant organisms that can be so controlled include MRSA, *Clostridium difficile* and multi resistant Gram-negatives. Implementation of a successful stewardship programme depends upon a local understanding of problem areas in prescribing and a multi disciplinary, long term educational commitment. Restrictive practices can also be very effective, perhaps particularly in the short term. Local initiatives need complimentary action on an infection control front and no hospital can consider itself isolated from the surrounding community nor, increasingly from the whole world.

Keywords Antibiotic stewardship • Resistance • Education • Restriction • Formularies • Pharmacists

Introduction

A lot of data has been published over the past decade on community antibiotic consumption, at least in Europe, where there are convincing data of some significant reductions in consumption at a Country-wide level (Sabuncu et al. 2009). Similarly banning use of antibiotics as growth promoters has led to major reduction in use per animal reared (Aarestrup et al. 2010). Other areas of use have less transparency of data, even in Europe and this applies also in the healthcare setting. The little available data indicates significant differences in levels of hospital use within different European countries, and also within hospitals depending upon case mix (MacKenzie et al. 2007). Intensive care units have the highest use, often double or treble the defined daily doses (DDDs) of the rest of the hospital.

I. M. Gould (✉)
Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, AB25 2ZN Aberdeen, Scotland
e-mail: i.m.gould@abdn.ac.uk

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_4, © Springer Science+Business Media, LLC 2011

Audits of quality of use repeatedly show inappropriate antibiotic prescribing much of it over prescribing, some under dosing. Overprescribing might mean unnecessary prescriptions, or prescription of an unnecessarily broad spectrum agent, or double or treble combinations (or even more!), sometimes termed spiralling therapeutic empiricism (MacKenzie et al. 2003; Kumarasamy et al. 2003). Whatever form it takes, inappropriate prescribing exerts ecological selection pressure on resistance. How to reduce this selection pressure by Stewardship is the subject for this chapter.

The Cochrane Review on Interventions to Control Antibiotic Prescribing in Hospitals, published in 2006, reviewed the English language literature up to the end of 2002 (Davey et al. 2005). Although over 200 such publications were available for review, only 66 met Cochrane criteria for inclusion as robust enough to allow safe conclusions to be drawn. Only a small number (13) of those 66 studies included robust enough data on microbiological outcomes to allow conclusions on changes in resistance rates, the majority suggesting reversal of cephalosporin resistance in Gram-negatives with reduction in cephalosporin use (Davey et al. 2006; Carling et al. 2003; Calil et al. 2001; Leverstien-van Hall et al. 2001; de Man et al. 2000; Landman et al. 1999; McNulty et al. 1997; Khan and Cheesbrough 2003; Bradley et al. 1999; de Champs et al. 1994; Gerding and Larson 1985; Climo et al. 1998; Pear et al. 1994; Lautenbach et al. 2003; Singh et al. 2000; Toltzis et al. 2002) (Table 1).

Recent Literature on Control of Resistance by Stewardship

In the last few years there has been a definite increase in interest in this area, as reflected by the published literature. The Cochrane review gave no reason for optimism that stewardship could reduce MRSA rates. Those with a knowledge of the role of antibiotics in causation of MRSA and the strength of predisposition to acquisition of MRSA that their use gives, were surprised by this. It is evident now that stewardship can have beneficial and clinically significant effects on rates of this organism. These studies are reviewed in Table 2 (Frank et al. 1997; Fukatsu et al. 1997; May et al. 2000; Keegan et al. 2002; Allegranzi et al. 2002; Geissier et al. 2003; Monnet et al. 2004; Hughes et al. 2004; Aubert et al. 2005; Martin et al. 2005; Charbonneau et al. 2006; Apisamthanarak et al. 2006; Bosso and Mauldin 2006; Madaras-Kelly et al. 2006; Cook et al. 2006; Avery and Ameerally 2006; Bassetti et al. 2006; Liebowitz and Blunt 2008; Aldeyab et al. 2008; Vernaz et al. 2008; Meyer et al. 2007; Buising et al. 2008). There is certainly a consistency of effect, albeit there may be a publication bias. It is consistently quinolones and cephalosporins whose reduction in use is associated with falling MRSA rates but this is plausible as they are two of the most commonly used groups of antibiotics in hospitals, and all epidemic hospital strains are resistant. The role of other β lactams, including lactamase inhibitor combinations is much less clear and there are theoretical reasons, to do with PBP binding specificity, why their use may not be as bad for MRSA rates. Clearly not all the published studies are robust enough to be included in a Cochrane review which only accepts well controlled studies and interrupted time series (ITS), but nevertheless, there are enough ITS to confirm this hypothesis.

Table 1 Robustness of published interventions to improve antibiotic prescribing in hospital: effects on antibiotic resistance. (Davey et al. 2005)

Interventions	Outcome	Good evidence	Weak evidence	No evidence
Restrictions of third generation cephalosporins	Resistant Gram –ve bacteria	Carling et al. 2003 de Man et al. 2000	Calil et al. 2001 Landman et al. 1999	Leverstien van Hall et al. 2001
	CDAD	Carling et al. 2003	McNulty et al. 1997 Khan and Cheesbrough 2003	
	MRSA			Carling et al. 2003 Landman et al. 1999
	VRE	Bradley et al. 1999		
Restriction of aminoglycosides	Resistant Gram –ve bacteria		de Champs et al. 1994 Gerding and Larson 1985	
Restriction of clindamycin	CDAD		Climo et al. 1998 Pear et al. 1994	
Restriction of vancomycin	VRE			Lautenbach et al. 2003
Reduced duration of antibiotics in ICU	Colonisation or infection by resistant Gram –ve bacteria	Singh et al. 2000		
Cycling of antibiotics in ICU				Toltzis et al. 2002

CDAD Clostridium difficile associated disease
MRSA methicillin resistant *Staphylococcus aureus*
VRE vancomycin-resistant enterococcus
ICU intensive care unit

Table 2 Antibiotic use and control of MRSA

Study	Design	Location	Intervention	Outcome
Frank et al. (1997)	UBA	Scandinavian Hospital-wide	↓3GC	↓MRSA ↓MRGNB
Fukatsu et al. (1997)	UBA	Japan Surgery	↓3GC +isolation	↓MRSA ↓ WI
Landman et al. (1999)	ITS (analysed as UBA)	USA Hospital-wide	↓3GC Clind, Vanc	ESBL→MRSA → ↑MR *Acinetobacter*
May et al. (2000)	ITS	USA	↓3GCs	↓MRSA (B and A) ↓ VRE
Keegan et al. (2002)	ITS (analysed as UBA)	USA Hospital-wide	↓ 4FQ 3GC, +hygiene	↓MRSA
Allegranzi et al. (2002)	UBA	Italy ICU	↓ Pip/Tazo ↓ Co-amoxi ↑ Cotrim, Imip ↑ Cefep	↓ MRSA ↑ Imip-R Pyo ↓ Pip-Taz-R Pyo
Carling et al. (2003)	ITS	USA Hospital-wide	Choice duration oral switch	↓ *C. dif* ↓ MRGNB → MRSA → VRE
Geissier et al. (2003)	UBA	France ICU	↓ 4FQ ↑ 3GC, Carbapenems	↓ MRSA
Monnet et al. (2004)	UBA	France ICU	↕ 4FQ 3GC ↕ Macrolides	↕ MRSA
Hughes et al. (2004)	CBA	USA	Rotation	↓ MRSA, MRGNB, ESBL, Total infection; GRE, VRE, *C. diff*
Aubert et al. (2005)	UBA	French ICU	4FQ	↓ MRSA ↓ MR Pyo
Martin et al. (2005)	ITS	US University Hospital-wide	↓3GCs	↓ MRSA
Charbonneau et al. (2006)	ITS	French Hospital-wide	↓ 4FQ	↓ MRSA
Apisamthanarak et al. (2006)	UBA	Thailand University Hospital	↑ 3GC ↓ 4FQ	↓ MRSA ↓ MRGNB
Bosso and Mauldin (2006)	ITS	USA University Hospital	↓ Cip ↑ Levo ↓ Levo ↑ Levo	↕ MRSA ↕ MRGNB
Madaras-Kelly et al. (2006)	ITS	USA Veterans Hospital	↓ 4FQ ↑3GC ↑Pip/Taz. Cotrim	↓ MRSA ↑ MRGNB
Cook et al. (2006)	ITS	US University Hospital-wide	↓ Cipro	↓MRSA

Table 2 (continued)

Study	Design	Location	Intervention	Outcome
Avery et al. (2006)	Obs	UK Max Fax Uni Hosp	Surg proph ↓2GC	↓MRSA
Bassetti et al. (2006)	UBA	Italy ICU University Hosp	↑4FQ ↓3GC	↑ESBL ↓MRSA
Meyer et al. (2007)	ITS	Germany	2GC Carbap BLIs ▼Glycopep	↓MRSA
Aldeyab et al. (2008)	ITS	UK Uni	↓3GC/4FQ Macro BLIs	↓MRSA
Vernaz et al. (2008)	ITS	Swiss Uni	↓3GC4FQ Macro BLIs	↓MRSA
Liebowitz and Blunt (2008)	ITS	UK DGH	↓Cipro/3GC	↓MRSA
Buising et al. (2008)	ITS	Australia	Glycopep ↑ ESP Carbap 3/4GC ▼Aminoglyc	MRSA MDR P. aerug ▼Cefaz ® *E. coli*

UBA Uncontrolled before after study
3GC 3rd-generation cephalosporin
ESBL extended spectrum β lactamase
ITS interrupted time series analysis
4FQ 4-fluroquinolone
VRE vancomycin resistant enterococci
↑ increase
MRSA methicillin resistant *Staphylococcus aureus*
↓ decrease
MRGNB multiple resistance Gram-negative bacilli
Pip/Tazo piperacillin/tazobactam
Pyo pyogenes
Co-amoxi co-amoxiclav
C. diff Clostridium difficile
Imip imipenem
Cefep cefepime
R resistance
Obs observational
Max fax maxillo facial
DGH district general hospital
Uni university
2GC 2nd generation cephalosporin
BLIs β lactamase inhibitors
Aminoglyc aminoglycoside
Cipro ciprofloxacin
Macro macrolide
Cefaz ceftazidime

Table 3 Interventions to improve antibiotic prescribing in hospital

Intervention	Outcome	Author	Country
Restriction of 3GCs	MRGNB	Martin et al. 2005	Korea
		Lan et al. 2003	Tunisia
		Lee et al. 2004	Taiwan
		Brahmi et al. 2006	USA
		Petrikos et al. 2007	Greece
		Buising et al. 2008	Australia
	CDAD	Ludlum et al. 1999	UK
		Fowler et al. 2007	UK
		Valiquette et al. 2007	Spain
3GCs	VRE	May et al. 2000	USA
Vanco		Fridkin et al. 2002	
Restriction of 4FQs	MRGNB	Aubert et al. 2005	France
		Madaras-Kelly et al. 2006	USA
	CDAD	Valiquette et al. 2007	Spain
Better lab reporting	CDAD	Bouza et al. 2004	Spain
		Bouza et al. 2007	
Cycling of antibiotics in the ICU	MRGNB/G	Hughes et al. 2004	USA
	PCs or CDAD	Martinez et al. 2006	Spain

3GCs 3rd-generation cephalosporin
MRGNB multiple resistance Gram-negative bacilli
Vanco vancomycin
CDAD Clostridium difficile associated disease
4FQs 4th generation cephalosporin
VRE vancomycin resistant enterococcus
ICU intensive care unit
GPCs Gram-positive cocci

Many other studies have now also shown the importance of modulations of other resistant organisms by antibiotic use (Table 3) (Buising et al. 2008; Lan et al. 2003; Lee et al. 2004; Brahmi et al. 2006; Petrikkos et al. 2007; Ludlam et al. 1999; Fowler et al. 2007; Valiquette et al. 2007; Fridkin et al. 2002; Bouza et al. 2004, 2007; Martinez et al. 2006). With the spread of plasmid mediated quinolone resistance, often linked to other major resistance determinants such as ESBLs, carbapenemases and aminoglycoside modifying enzymes, the importance of these findings can't be over emphasised. Likewise, the role of reducing use of 3GCs in controlling ESBLs has become clearer. For *Clostridium difficile*, it is important to realise that resistance to quinolones and macrolides-lincosamides is acquired and resistance to 3GCs is innate. The section on cycling is not meant to be complete. Indeed current concepts favour diversity as a better way to reduce emergence of resistance.

Stewardship: How to Do It

A lot can be learnt from the Cochrane review but many unanswered questions remain (Davey et al. 2005). There is little evidence to support any single type of intervention over another. Most can be classified into educational, often performed

Table 4 Core elements of antimicrobial stewardship programmes. (Dellit et al. 2007)

Tactic	Level of evidence	Comment
Prospective audit with interventions (feedback)	A-I	Core activity for AMT
Guidelines and clinical pathways	A-I	Core activity, but implementation plans are critical
Formulary restriction and pre-authorisation	A-II	Core activity but may just squeeze the balloon
PK/PD dose optimisation	A-II	Improves outcome Prevents resistance
Streamlining or de-escalation	A-II	Reduces use of broad spectrum agents
Intravenous to oral switch	A-III	Reduces costs and length of intravenous access May not help with resistance per se
Education	A-III	Critical, but must be ongoing and interactive
Antimicrobial order forms	B-II	Focuses decision making Shortens duration of treatment
Combination therapy/cycling	C-II	Increase antibiotic exposure Mainly theoretical benefit Likely to be most beneficial at start of treatment

PK/PD pharmacokinetic/pharmacodynamic CID 2007 44 159

by pharmacists, or restrictive, often performed by physicians. Speed and size of impact of the intervention and its longevity (sustainability) are areas that need further study. Structural and organisational interventions such as computerised prescribing and antimicrobial teams are being implemented more and more, the latter often including antimicrobial pharmacists although specialty training for them is in its infancy outside of the USA. Core elements of a Stewardship Programme are shown in Table 4 (Dellit et al. 2007).

Implementation of a Stewardship Programme

Pragmatically the first thing to do is audit to establish areas of poor prescribing practice, high levels of antibiotic resistance and/or large consumption of antibiotics, not forgetting that poor infection control can magnify the effects of poor prescribing. All these areas are time/resource consuming. Even more difficult is to set in motion the cycle of changing practice with re-audit to confirm or refute benefits of the interventions.

If the hospital has no prior experience, it can be quite difficult to set up automated systems for measurement of antibiotic consumption and its reporting in relation to a measure of hospital activity. Generally, WHO Defined Daily Doses (DDD) per 100 Occupied Bed Days (OBD) is the Internationally recommended method of measurement and this allows benchmarking with other units and hospitals (MacK-

enzie and Gould 2005). Good quality laboratory data on antibiotic susceptibility is also important, ideally reported by minimum inhibitory concentration (MIC) by an internationally recommended method such as CLSI (Clinical and Laboratory Standards Institute 2009) or EUCAST (http://www.EUCAST.org) which will allow both comparisons with other units and also detection of subtle trends in susceptibility.

Robust methods of evaluation of interventions are also important, not only so that proper assessment of their efficacy can be made to enable concentration of scarce resource on the most effective interventions, but also so that work can be published to add to the scarce body of literature in this area. Essentially this means performing ITS which requires at least three (and ideally at least 12) data points before and after the intervention (Davey et al. 2005). Usually, monthly data points are satisfactory for a medium size hospital, both for DDD/100 0BD and for number or percent resistant of any of the common bacterial pathogens.

Performance of audits of detailed quality of use are more difficult to report in publishable form but point prevalence surveys of several hospitals in a region or country, performed at regular intervals, can provide reasonable quality indicators of progress in this difficult area (Seaton 2007).

It is difficult to generalise from the literature and say which are the most likely areas of poor quality/high volume prescribing and which are liable to the most successful interventions. These will very much depend on local factors, personalities and relationships. Barriers to success, counter measures, cultural elements and resource all have to be assessed locally and priorities decided. Interventions are likely to need to be continuous or at least long term, and support from the hospital executive is likely to be beneficial. It is easy to be too ambitious and implement many interventions on a broad front, at risk that they won't be sustainable. On the other hand, any single intervention is unlikely to have a major effect. Patience, long term commitment and resource are all required (van der Meer and Grol 2007).

Common Problems in Antibiotic Prescribing

Surgical prophylaxis is a common area of overuse as shown in many publications. Measured by total DDDs, it can amount to around one third of a hospitals total antibiotic use. This illustrates the potential for ecological damage although surgeons often ask whether 24 h or even single dose prophylaxis can really select for resistance. The simple answer is yes, but of course much of the problem is extension of prophylaxis beyond the perioperative period, often for several days in critical patients, perhaps until all lines and drains are removed. There is no evidence base in favour of such practices. The Royal College of Physicians in Edinburgh publishes an updated evidence based guideline at http://www.sign.ac.uk.

Since the first publication of British and American guidelines on management of community acquired pneumonia (CAP), audits have repeatedly shown over enthusiastic implementation of their rather aggressive non-evidenced based treatment guidelines (Kumarasamy et al. 2003). This has resulted in huge increases in use of

broad spectrum β lactams often in combination with macrolides. Quinolones too, are increasingly used. While the guidelines reserve such recommendations for the more seriously ill, clinicians often err on the side of caution and these aggressive regimens are prescribed for many minor infections. The recommendations come from an apparent desire amongst the guideline writers to offer as broad spectrum cover as possible in treatment of CAP which has many possible aetiologies, including antibiotic resistant variants of pneumococci, as well as (rarely) Gram-negatives or mixed or atypical infections. There is no evidence base that such complex regimens improve outcome but they have certainly increased hospital antibiotic use. Many believe they are the single most important cause of current epidemics of MRSA, *Clostridium difficile* and other multi-resistant organisms. All along, high dose penicillin would have been satisfactory for most of these infections (Bonten and Oosterheert 2007) and this is reflected now in the recent change in pneumococcal breakpoints by CLSI which now considers penicillin treatment suitable for virtually all non-meningeal pneumococcal infections.

Complex surgical patients who develop sequential problems, often potentially infective, are another area of antibiotic abuse, commonly in the form of spiralling therapeutic empiricism. Antibiotics are added to cope with each new supposed/possible infection, often with no laboratory cultures to confirm the need for antibiotics and this results in simultaneous treatment with several increasingly broad spectrum antibacterials, often in combination with antifungals to prevent against the consequent invasive fungal disease. Use of combination therapy is now being questioned in many areas as the clinical benefits remain unclear and toxicity of the use of agents such as an aminoglycoside or rifampicin are all too evident (Forrest and Tamura 2010).

Use of the Laboratory to Improve Prescribing

There are many ways in which the laboratory can help in antibiotic stewardship. Most obviously, the rapid and accurate reporting of culture and susceptibility testing (Fowler et al. 2007), along with MICs where PK/PD optimised dosing schedules might give critical benefit such as for multi resistant infections in the ICU. This approach can also be utilised to stimulate stepdown/streamlining/oral switch and other rationalisations of initial broad spectrum, often complex, empiric regimens. These empiric regimens can be informed by, amongst other things, cumulative susceptibility results, ideally by patient catchment area such as primary care, nursing home, intensive care etc which can form the rationale for local antibiotic formularies (lists of drugs) and policies (Richet 2005).

Therapeutic monitoring for agents with narrow therapeutic margins, like aminoglycosides and glycopeptides, can ensure both appropriate dosing, and also regulation of use to essential indications only. Consultation by clinically trained laboratory staff, based on requests for such serum assays or stimulated by the need for rapid reporting of positive blood cultures or growth of unusual organisms/isolates

from sterile sites can be used both for immediate patient benefit and also for building of contacts which stimulate requests for further consults.

In liaison with pharmacists and physicians specially trained in antimicrobial prescribing, the laboratory can become a key player in multidisciplinary antimicrobial teams (AMT), the "Gatekeepers" of antibiotics, but also the educators (Knox et al. 2005). This is a critical ongoing function of AMT's for all postgraduate groups involved in antibiotic prescribing, including most if not all doctors, and increasingly nurses and pharmacists themselves. Some have even suggested that, in future, anyone able to prescribe antibiotics must have undergone formal postgraduate education in this area, with regular appraisal and revalidation.

New laboratory developments suggest that pro-inflammatory cytokines and procalcitonin (Gilbert 2010) may offer useful indication of bacterial infection, allowing early cessation of antibiotic or, indeed, withholding of antibiotics from certain patients. Screening for carriage of multi resistant organisms such as MRSA or ESBL, which have a high likelihood of developing into infection, can not only inform empiric therapy directed against the organism but also, at least for MRSA, indicate that cephalosporins, quinolones or other agents to which the MRSA is resistant should not be prescribed as they might encourage overgrowth of the MRSA or even enhanced virulence.

After Word

With 30 years of battling against antibiotic misuse it is heartening to have been practising in the last 2 years when the effects of political interest in the rising tide of HAI, and in particular in MRSA and *C. difficile* have seen both resource and, just as importantly, Executive action directed at antibiotic stewardship. With Central Government direction for programmes, resource and sanctions, more has been achieved in this short space of time than in the previous 28 years of professionally led education. Whether this is sustainable of course, remains to be seen but there seems to be nothing as powerful as Administrative and Financial sanctions of Hospital Chief Executives and Medical Managers to alter doctors attitudes to guidelines. As a result, in our hospital and nationwide we have seen huge reductions (>50%) in quinolone and cephalosporin use in the past 2 years rapidly followed by massive falls in *C. difficile*rates (over 50%). The message is to get medical leadership to buy into stewardship.

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Controlling *Clostridium difficile* Infection and the Role of Antibiotic Stewardship

Ed J. Kuijper, S. Johnson, A. Goorhuis and M. H. Wilcox

Abstract Since 2002, increasing rates of nosocomial *Clostridium difficile* infection (CDI) with a more severe course, higher mortality, and more complications have been reported in Canada, USA and Europe. One specific strain (PCR ribotype 027, REA-group BI, PFGE-type NAP1) was identified and accounted for at least half of the isolates. CDI can be prevented by robust infection control practice and prudent antibiotic use. In an outbreak setting it is often practical to combine multiple different CDI interventions which may consist of increased and early case finding, expanded infection-control measures, and antibiotic stewardship. Antimicrobials to be targeted ideally should be based on the local epidemiology and the *C. difficile* strains present, but restricting the use of cephalosporins and clindamycin have been the most effective. The results of fluoroquinolone restriction have been varied and may be of particular importance for outbreaks associated with the hyper-virulent PCR ribotype 027 strains.

Keywords Antibiotic associated diarrhea • Metronidazole • Vancomycin • Toxin • Gut flora • Colostrum

Introduction

In 1978, *Clostridium difficile* was recognized as the causative agent of antimicrobial associated diarrhoea, colitis and pseudomembranous colitis in humans. Since then, *C. difficile* emerged as an important enteropathogen because of its association with healthcare and impact on morbidity and mortality in the elderly. *C. difficile* is an anaerobic bacterium, widely distributed in soil and in the intestinal tracts of animals. Its vegetative cells are capable of forming spores, which confer resistance to heating, drying and chemical agents, including disinfectants. Colonic injury and inflammation result from the production of two protein toxins: enterotoxin A (TcdA; 308,000 Mr) and cytotoxin B (TcdB; 270,000 Mr). Genes for the binary toxin are located outside the pathogenicity locus (PaLoc), but the role of this toxin is unclear

E. J. Kuijper (✉)
Department of Medical Microbiology, Leiden University Medical Center (LUMC), Albinusdreef 2, 2333 ZA, Leiden, The Netherlands
e-mail: E.J.Kuijper@lumc.nl

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_5, © Springer Science+Business Media, LLC 2011

(Kuijper et al. 2007). Currently, PCR ribotyping is considered to be the standard method for typing of *C. difficile* in Europe (Kuijper et al. 2009). This method has since been used routinely by the UK Anaerobe Reference Laboratory in Cardiff and subsequently by the Health Protection Agency's *C. difficile* Ribotyping Network for England and N. Ireland. From nearly 10,000 isolates from all sources examined, a library that currently consists of over 450 distinct PCR ribotypes has been constructed. PCR ribotyping correlates well with lineages build by whole genome sequencing (He et al. 2010). Phylogenetic analysis demonstrates *C. difficile* is a genetically diverse species, which has evolved within the last 1.1–85 million years. Disease associated isolates emerged from multiple phylogenetic lineages, contradicting the idea that a single lineage evolved to become pathogenic. Highly epidemic and disease-causing isolates are found in all lineages, suggesting there may be certain genetic elements common to all *C. difficile* strains that are associated with virulence (He et al. 2010).

The illness associated with *C. difficile* ranges from mild diarrhoea to life-threatening colitis (Bartlett 2002). Typical clinical features include diarrhoea, lower abdominal pain and systemic symptoms such as fever, anorexia, nausea and malaise. Fulminant colitis occurs among 1–3% of patients and is characterized by signs and symptoms of severe toxicity with fever and diffuse abdominal pain and distention. Cases of fulminant colitis could result in fatal disease, due to bowel perforation and peritonitis. Pseudomembranous colitis represents an advanced stage of disease, and this finding on endoscopy is highly suggestive of CDI. Severely ill patients may have little or no diarrhoea as a result of toxic dilatation of the colon (toxic megacolon) and paralytic ileus. Toxic megacolon may be associated with severe sepsis and multiple organ dysfunctions. Mortality associated with toxic megacolon is high, ranging from 25 to 40%. Recurrent diarrhoea is seen in 5–40% of patients (typically 20–25%).

CDI as Healthcare Associated Infection

CDI is primarily a nosocomial disease that can be prevented by robust infection control practice and prudent antibiotic use. CDI is currently the most frequently occurring nosocomial infection in some European hospitals and has the potential to become the most frequent in others if appropriate surveillance, prevention and control measures are not implemented (Kuijper et al. 2006). The elderly and immunocompromised are particularly at risk. The proportion of the population in these high-risk groups is increasing with the general ageing of the population in Europe. The impact of CDI in healthcare settings is considerable. Affected patients require isolation, supportive therapy for underlying disease and specific therapy for CDI, scrupulous hygiene in nursing, environmental decontamination, and (in outbreaks) ward closure. The financial impact of CDI on the healthcare system is substantial (5–15,000 €/case in England and $ 1.1 billion/year in the USA). Assuming a European Union population of 457 million, the potential cost of CDI can be estimated to

be 3,000 million €/year, and is expected to almost double over the next four decades (Kuijper et al. 2006).

Since 2002, increasing rates of CDI with a more severe course, higher mortality (from 4.7 to 13.8%) and more complications (from 7.1 to 18.2%) have been reported in Canada (Pepin et al. 2005; Loo et al. 2005), USA (McDonald et al. 2005) and Europe (Kuijper et al. 2006). One specific strain was identified and accounted for at least half of the isolates. This strain belongs to REA-group BI, PFGE-type NAP1, toxinotytpe III, and PCR ribotype 027. It also contains genes for binary toxin as well as the major virulence factors, toxins A and B and a deletion of 18 bp in the *tcd*C gene which is a negative regulator of toxin A and B. This strain was first described in a woman with severe pseudomembranous colitis in 1988, and identified as strain CD196 (Popoff et al. 1988). In 2008, *C. difficile* PCR ribotype 027 was detected in 16 European countries (Kuijper et al. 2008).

The epidemiology of CDI is continuously changing. Recently, a European surveillance study has been performed in 34 European countries (Bauer et al. 2011 submitted). CDI incidence varied across hospitals (mean: 5.5 per 10,000 patient-days per hospital; range: 0–36.3). In 2005, Barbut et al. (2007) observed a mean incidence of nosocomial CDI in 23 European hospitals of 2.45 per 10,000 patient-days, with a range from 0.13 to 7.1, which is lower than the overall figure of 5.5 per 10,000 patient-days in the most recent study. Clearly, CDI is an important nosocomial infection and is still increasing in frequency in some countries. This increase is not associated with type 027 only. An increase of CDI caused by another strain, PCR-ribotype 078 (toxinotype V) has been noted in The Netherlands (Goorhuis et al. 2008). At present, it is the second most frequently encountered type (Hensgens et al. 2009, 2010). Diarrhoea caused by Type 078 presents as severe as 027-CDI, but affects a younger population and has a higher frequency of community-associated disease (Goorhuis et al. 2008). The recently completed surveillance study in 34 European countries mentioned earlier, revealed that type 078 is currently the third most frequently encountered ribotype strain in Europe.

Infection Control Measures

C. difficile is the leading cause of intestinal infections related to antimicrobial therapy. Factors that may also predispose for CDI include increased age, bed occupancy rate (Kaier et al. 2010) and duration of hospital stay, previous hospitalization, intensive care stay, severe comorbidity, immunosuppressive agents, and severity of underlying diseases (Kuijper et al. 2007; Vonberg et al. 2008). The role of proton pump inhibitors and other antacids in CDI development is still a matter of debate. Direct or indirect contact represents the main route of *C. difficile* transmission, as spores may persist in the environment for months or years and show resistance to various environmental cleaners such as detergents and some disinfectants. Limited information is available regarding the intestinal carriage, frequency of skin contamination and environmental shedding of *C. difficile* during and after treatment of

CDI. A recently performed study encompassing 52 patients with CDI revealed that, 1–4 weeks after treatment, 56% of patients were still carriers of *C. difficile* (Sethi et al. 2010). The frequencies of skin contamination and environmental shedding remained high at the time of resolution of diarrhoea (60 and 37%, respectively), were lower at the end of treatment (32 and 14%, respectively), and again increased 1–4 weeks after treatment (58 and 50%, respectively). These results provide support for continuation of isolation and contact precautions after resolution of diarrhoea. The role of asymptomatic carriers as a potential source for transmission of epidemic and nonepidemic *C. difficile* strains among long-term care facility residents, is unknown although one study found surprisingly high levels of skin contamination in asymptomatic patients (Riggs et al. 2007). The possibility of transmission via the airborne route has been suggested recently by two studies; the potential for the dispersal of *C. difficile* spores in air needs further exploration, especially in outbreak situations (Best et al. 2010; Roberts et al. 2008). A frequently underestimated risk factor for the development of CDI concerns "CDI pressure" (Dubberke et al. 2007a, b). CDI pressure, a modified version of colonization pressure, is defined as the sum of a patient's daily exposure to patients with CDI who share the same unit or ward divided by the patient's length of stay at risk. Increasing CDI pressure has been found as a strong risk factor for development of CDI (Dubberke et al. 2007a, b). CDI pressure has been studied in relation to symptomatic CDI cases only and additional studies are needed to establish the importance of asymptomatic *C. difficile* carriers on the transmission of CDI.

Evidence-based guidelines to limit the spread of *C. difficile* has been summarized by Vonberg et al. (2008) and have also been provided by IDSA and SHEA (Cohen et al. 2010). The recommendations encompass early diagnosis of CDI, surveillance of CDI, education of staff, appropriate use of isolation precautions, hand hygiene, protective clothing, cleaning and disinfection with a sporicidal agent of the environment and medical equipment, and specific measures during outbreaks such as closure of wards to new admissions, cohort isolation of patients and, if indicated, use of vaporized H_2O_2 in vacated patient rooms (although the practicality and cost-effectiveness of this approach is unclear). An additional key to CDI prevention is to reduce the number of susceptible patients. This can result from good antimicrobial stewardship, which will minimise the antimicrobial exposure of patients in the hospital, thus reducing the number of patients susceptible to developing CDI even if *C. difficile* transmission occurs Vonberg et al. 2008; Cohen et al. 2010).

Antibiotics and CDI

The human GI tract microbiota is composed of numerous uncultured microbes and predominated by Firmicutes, Bacteroidetes and Actinobacteria (Zoetendal et al. 2008). In healthy adults the human GI tract microbiota fluctuates around a stable individual core of species that are affected by host genetics, environmental and stochastic factors. The microbiotia is estimated to consist of up to 1,000 species per

individual. Exposure to antibiotics is believed to lead to disturbance of the normal gastrointestinal microbiota. This may predispose to diarrhoea after acquisition (or selection) and proliferation of toxinogenic *C. difficile*. The bacterial species belonging to the microbiota that confer protection against colonization with *C. difficile* are unknown but are currently under investigation using sequencing and small subunit ribosomal RNA (SSU rRNA) based microarrays. Restoration of protective intestinal flora is likely critical for preventing CDI recurrences following successful treatment, particularly among patients with multiple recurrent CDI episodes. A recently published review summarised the literature regarding successful treatment with donor faeces for recurrent CDI (van Nood et al. 2009).

Of all patients who develop CDI in the hospital setting, approximately 80–90% have used antibiotics in the previous 3 months. Almost any antibiotic may induce CDI, but broad-spectrum cephalosporins (in particular, second- and third-generation cephalosporins), and clindamycin are most frequently implicated. Ureidopenicillins (with or without β-lactamase inhibitors), cotrimoxazole and aminoglycosides appear to have a low propensity to induce CDI. The association of CDI with a particular antimicrobial agent may depend on several factors, including frequency of use in a institutional setting, effect of the antibiotic on the indigenous microbiota of the host, and susceptibility of particular *C. difficile* strains to that antibiotic. All three of these factors likely explained hospital outbreaks of CDI caused by REA group J strains (PCR ribotype 001) in the early 1990s in the United States (Johnson et al. 1999). This strain was responsible for outbreaks in four U.S. hospitals widely separated geographically and was highly resistant to clindamycin (MIC > 256 μg/ml), whereas only 15% of the non-epidemic strains in those hospitals were resistant. Use of clindamycin was significantly associated with CDI due to the J strain compared with CDI due to non-epidemic strains. In addition, clindamycin treatment in the hamster model renders the host susceptible to infection with *C. difficile* for weeks compared to days or less following treatment with other antibiotics and is likely due to the profound and lasting effect of clindamycin on the indigenous microbiota (Merrigan et al. 2003). Unlike the heterogeneous susceptibility patterns to clindamycin, most *C. difficile* strains are resistant to broad-spectrum cephalosporins, which may partially explain why these agents are also high risk agents for precipitating CDI.

Since 2000, fluoroquinolones have also been identified as a risk-factor for CDI, particularly in association with the hyper-virulent PCR ribotype 027. The type 027 strain of *C. difficile* is highly resistant to fluoroquinolones, particularly the newer respiratory fluoroquinolones, whereas historical (1980s–1990s) *C. difficile* PCR ribotype 027 isolates are more susceptible to these antibiotics (McDonald et al. 2005). Fluoroquinolone resistance can easily be induced *in vitro* (Spigaglia et al. 2009) and increased MICs of levofloxacin and/or moxifloxacin are associated with specific substitutions in GyrA and/or GyrB. In a recently published review, 11 studies on the role of fluoroquinolones as risk factor for CDI were analysed (Freeman et al. 2010). The odds ratio for fluoroquinolones calculated was 12.8, whereas the odds ratio for cephalosporins was 5.1. *C. difficile* ribotype 027 was involved in six of the outbreaks. No association with a specific fluoroquinolone was found, but

most studies did not perform this analysis. Using data from the National Reference Laboratory of CDI in The Netherlands (Goorhuis et al. 2007), fluoroquinolones were significantly associated with CDI due to type 027 (OR 2.88; 1.0–8.2) but not with CDI due to other strains. In contrast to the risk of fluoroquinolones during outbreaks of CDI due to type 027, fluoroquinolones were not associated with CDI in an endemic situation in which type 027 was not present. During a 34-months prospective case-control study in an academic hospital in The Netherlands, 93 CDI patients were diagnosed. CDI incidence was 17.5 per 10,000 admissions and the most frequently found PCR ribotypes were 001, 014/020, and 078. Therapeutic use of second and third generation cephalosporins, but not fluoroquinolones were recognized as risk factors (Hensgens et al. 2011). There are inconsistencies however in the literature. For example, Valiquette et al. achieved control of a CDI outbreak despite a marked increase (79%) in the prescribing of respiratory fuoroquinolones (Valiquette et al. 2007).

A recently performed point prevalence study among 41 hospitals in The Netherlands revealed that 6.2% of the patients had an nosocomial infection. On the day of the survey, 30.9% of the patients were receiving antibiotics (van der Kooi et al. 2010). The use of antibiotics differed considerably between hospitals. A study of the relationship between CDI incidence and the preceding use of different antibiotic classes at the hospital level (van der Kooi et al. 2008) in The Netherlands, showed statistically significant associations between the type 027-associated CDI incidence in hospitals and the (hospital-wide) total use of the studied antibiotics, the use of second-generation cephalosporins and the use of macrolides. However, the relative risks were very small. Interestingly, in the pre-epidemic period, the total use of the studied antibiotics was comparable between CDI type 027-affected and unaffected hospitals. The incidence of CDI varies with different departments in the hospital, likely due to variations in underlying disease and age of patients, prescribed medication and local presence of *C. difficile* spores. Therefore, an association of CDI incidence with local antibiotic use in specific departments may be of more importance than antibiotic use at hospital level. A similar study in northern France comparing antibiotic consumption between hospitals affected by *C. difficile* type 027 and those unaffected, revealed fluoroquinolones and imipenem use was highly associated with 027-affected hospitals in the multivariate analysis, suggesting that those antibiotics should be preferentially targeted by prevention campaigns in affected hospitals (Birgand et al. 2010).

The widespread use of antimicrobial agents, frequent administration of broad spectrum agents and the tendency to prescribe combinations of antibiotics mean that a precise quantification of the CDI risk associated with specific antibiotics is difficult. It is considered that the risk of CDI increases when a greater number of antimicrobial agents is administered, or greater number of doses or a greater duration of administration. Restricted use of certain high risk antimicrobials is a common strategy for reducing CDI rates. Antibiotic prescribing intervention studies have been used to examine prospectively the effects of a prescribing change upon CDI rates. A Cochrane 2005 review of interventions (1980–2003) to improve antibiotic prescribing practises found five studies designed to assess the impact of prescribing changes

upon rates of CDI, but only three showed a significant reduction in CDI (Davey et al. 2005). An important complicating factor in analysing prescribing antibiotic intervention studies is that that they frequently do not consider exposure to *C. difficile* when assessing outcomes. Implementation of other infection control interventions may also confound the interpretation of these studies. In an outbreak setting it is often practical to combine multiple different CDI interventions using an "infection control bundle" which may consist of increased and early case finding, expanded infection-control measures, and antibiotical stewardship. An optimal antibiotic stewardship program should encompass reducing unnecessary antimicrobial use, reducing the duration of antimicrobial use, reducing "redundant" antimicrobial therapy, and switching from parenteral therapy to oral therapy. However, the impact of using oral versus intravenous antibiotics in the context of CDI has not been fully evaluated. Antimicrobials to be targeted ideally should be based on the local epidemiology and the *C. difficile* strains present, but restricting the use of cephalosporins and clindamycin have been the most effective. The results of fluoroquinolone restriction have been varied. Two reports documented the effect of 'with-in-class' formulary switches of fluroquinolone agents after noting increased CDI rates when replacing levofloxacin with a newer fluoroquinolone. Gaynes et al. documented a decrease in CDI rates when they switched back to levofloxacin from gatifloxacin in their long-term care facility (Gaynes et al. 2004), whereas Biller et al. did not see a decrease when they switched back to levofloxacin from moxifloxacin at their community hospital (Biller et al. 2007). In the latter study it should be noted that total antibiotic prescribing continued to increase during the study period. It is possible that restricting antibiotic prescribing overall or this whole class of antibiotics is important in controlling outbreaks due to the 027 strain. Kallen et al. temporarily restricted all fluoroquinolones in their hospital and decreased CDI rates were seen, but this study was somewhat confounded by a change in the environmental services contractor shortly after implementation of the antibiotic intervention (Kallen et al. 2009). Debast et al. ended an outbreak of *C. difficile* type 027 by complete banning of the use of ciprofloxacin and restricting the use of cephalosporines (Debast et al. 2009).

Using the "infection control bundle" approach in Pittsburgh during an outbreak of CDI type 027, a rate reduction of 71% (odds ratio, 3.5; 95% confidence interval, 2.3–5.4; $P<0.001$) was obtained (Muto et al. 2007). Valiquette et al. introduced a number of measures to control an epidemic of nosocomial CDI caused by type 027 in Quebec and used interrupted time-series analysis to evaluate the impact of these measures on CDI incidence (Valiquette et al. 2007). No change in CDI incidence was noted after strengthening of infection control procedures, but implementation of the antimicrobial stewardship program was followed by a marked reduction in incidence Although Muto, Debast and Valiquette suggested that antimicrobial stewardship was more important than infection control measurements, Salgado et al. found achieved sustained control of a CDI outbreak using enhanced infection control measurements without formulary changes or new antibiotic control policies (Salgado et al. 2009).

In conclusion, CDI outbreaks are often multifactorial in terms of cause, the prevention and control of outbreaks should probably involve multiple interventions

aimed at improving antimicrobial use across the health care system and in individual patients, as well as interventions targeting environment control, personnel hand hygiene, and barrier precautions.

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The Control of MRSA

Evelina Tacconelli and G. De Angelis

Abstract The control of methicillin-resistant *Staphylococcus aureus* (MRSA) has been largely debated and it is still a controversial issue in many hospitals worldwide. In 2008, the European Antimicrobial Resistance Surveillance System (EARSS) reported an increased incidence of MRSA bacteraemia compared to 2007 (4.8 *versus* 3.5 per 100,000 patient-days), despite a decreasing trend in MRSA proportion across several European countries. Control measures used to reduce the prevalence of hospital-acquired infections due to MRSA include implementation of hand hygiene, active surveillance cultures, screening at hospital admission and discharge, pre-emptive and contact isolation, cohorting, decolonisation, and antibiotic stewardship. Implementation of hand hygiene has been proven as one of the most effective strategy in the control of MRSA, while the role of screening is still controversial. Recent data showed that decolonisation with mupirocin nasal ointment and chlorhexidine soap before surgical procedures reduces the incidence of *S. aureus* infections, including surgical site infections. Regardless the lack of robust evidence clearly in favour of a specific control measure, at the moment, the best program to control MRSA spreading in hospital and community has to include a multifaceted approach, involving infectious diseases physicians, microbiologists, pharmacists and public health officers.

Keywords Screening • HAI • CAMRSA • SAB • Mupirocin • Risk assessment

Introduction

In 2008, the European Antimicrobial Resistance Surveillance System (EARSS), a free network that connects more than 900 laboratories in 33 European countries, reported an increased incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia compared to 2007 (4.8 *versus* 3.5 per 100,000 patient-days), ranging from 0.2 in The Netherlands to 28.3 in Portugal. Nevertheless, numerous European countries have documented a reduced proportion of methicillin-resistance among *S. aureus* invasive isolates (EARSS annual report 2008). Few data are avail-

E. Tacconelli (✉)
Department Infectious Diseases, Università Cattolica, Rome, Italy
e-mail: etacconelli@rm.unicatt.it

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_6,

able on the real prevalence of MRSA in the community. The "true" community acquisition in healthy individuals without known predisposing risk factors is less frequently described. Community-acquired MRSA USA300 clone (ST8-IV) predominates over the United States, whereas community-associated MRSA in Europe is characterized by clone heterogeneity. The most common European strain is the European clone ST80, harbouring the staphylococcal cassette IV; nevertheless, USA300 strains are increasingly reported in Europe (Otter and French 2010). The control measures that are used to reduce the prevalence of hospital-acquired infections due to MRSA include implementation of hand hygiene, active surveillance cultures, screening at hospital admission, pre-emptive isolation of high-risk patients, decolonisation therapy, contact isolation, and antibiotic stewardship. None of these interventions was demonstrated to be effective where singularly administrated. Based on the available evidence, multifaceted approaches are more efficacious than single intervention. Indeed, some northern European countries have implemented nationwide control measures maintaining level of MRSA steadily less than 0.5%. This strategy, known as "search and destroy" (Vos et al. 2005), includes contact isolation for MRSA-positive patients; pre-emptive isolation and screening for high risk patients; screening of patients and personnel following an unexpected case of MRSA in the ward; screening of health care workers (HCWs) with suspension of those found to be carriers until decontamination is achieved; closure of wards to new admissions if there is more than one carrier among hospitalised patients. Bootsma et al. (2006) showed by a stochastic hospital model that the application of the search and destroy strategy in a hospital with high endemicity would reduce the prevalence to less than 1% within 6 years.

Hand Hygiene

Over the last decades several studies have confirmed the importance of hand hygiene to prevent the transmission of several pathogens, including MRSA, from the hands of HCWs to patients. Diabetes, dialysis and skin lesions are likely to increase the risk of skin colonisation by MRSA. There are few studies addressing the real prevalence of MRSA on HCWs hands. Pittet et al. (1999) reported a 10.5% of culture positive for *S. aureus* and a linear increase of bacterial contamination on HCWs hands during patient care. One study conducted in a tertiary hospital in Ireland documented that 5% of fingertips from more than 500 HCWs were positive for MRSA, also after hand hygiene was performed (Creamer et al. 2010). Pittet et al. showed a better performance of alcohol-based hand rub (ABHR) in reducing the level of contamination whereas Creamer showed a similar benefit of ABHR and hand washing with soap and water. In both studies the rate of contamination was higher after close patient contact and contact with body fluid secretions. It is important to underline that the use of gloves does not protect against hand contamination. Recently, universal gloving with emollient-impregnated gloves was associated with improved hand hygiene compliance and skin health (Bearman et al. 2010).

Several studies have documented the efficacy of hand hygiene promotion on the rate of healthcare-associated infections. Pittet et al. (2000) monitored the overall compliance with hand hygiene during routine patient care in a teaching hospital in Geneva, Switzerland, before and during implementation of a hand hygiene campaign. Compliance significantly improved from 48% in 1994 to 66% in 1997, coinciding with a reduction of nosocomial infection rate and new hospital-acquired MRSA cases. Numerous studies have documented the *in vivo* antimicrobial activity of alcohol. A recent systematic review showed that ABHRs remove organisms more effectively, require less time, and irritate skin less often than hand washing with soap or other antiseptic agents and water (Picheansathian 2004). Fitting a multivariate time-series analysis, Kaier et al. (2009) demonstrated that a higher volume of use of ABHR was associated with a lower incidence of nosocomial MRSA infection. Recently published World Health Organisation (WHO) guidelines on Hand Hygiene in Health Care recommends hand washing with soap and water when hands are visibly dirty or visibly soiled with blood and other body fluid, and if exposure to potential spore-forming pathogens (*Clostridium difficile*) is strongly suspected or proven, while use of ABHR should be preferred for routine hand antisepsis in all other clinical situations (WHO guidelines 2009).

MRSA Surveillance and Screening

A recent systematic review of the literature performed by McGinigle et al. (2008) summarized the evidence of the efficacy of active surveillance cultures in the intensive care unit (ICU) setting on several clinical and economic outcomes. Although most of observational studies reported a significant reduction in MRSA infections after the application of active screening, the evidence was of poor quality and could not allow definitive recommendations. The limit of the available evidence mainly relies on the lack of studies focused only on screening. Indeed, in studies of infection control measures, screening is never the primary intervention and it is usually included in a multifaceted approach. 'Who', 'where' and 'when' should be screened for MRSA are still open questions. However, despite controversial evidence, six USA States have introduced mandatory universal screening for MRSA at hospital admissions and a further eight are waiting for approval. Similarly, the English Department of Health has introduced mandatory universal screening to all patients admitted to National Health Service hospitals. Screening was to be in place for all elective admissions by March 2009, and for all admission by December 2010. One of the most cited experience in favour of the introduction of universal screening for MRSA at hospital admission is a large prospective cohort study performed in three affiliated hospitals in the USA (Robicsek et al. 2008). The introduction of universal admission surveillance for MRSA was associated with a large reduction in MRSA disease compared to baseline period during which no screening for MRSA was performed. On the other hand, many studies could not prove a significant reduction in MRSA infection after the introduction of universal screening. Harbarth et al.

(2008) could not show a significant reduction of nosocomial MRSA infection rate in a prospective interventional crossover study after the introduction of universal MRSA admission screening in a large cohort of surgical patients. Targeted screening might have a cost-effectiveness approach. Harbarth et al. (2006b) defined as risk factors for unknown carriage of MRSA at hospital admission in a university hospital in Geneva the following variables: male sex, age >75 years, previous exposure to quinolones, cephalosporins and carbapenems, previous hospitalisation, intra-hospital transfer and urinary catheterisation. Haley et al. (2007) performed a 7-week study during which all patients upon admission to and discharge from the general internal medicine floor of a community hospital were screened by anterior nares surveillance cultures. Logistic regression analysis revealed three independent risk measures for MRSA at admission: a nursing home stay, prior MRSA infection, and the combined effects of homelessness, jail stay, promiscuity, intravenous drug use, and other drug use. Numerous studies have reported control of MRSA with screening linked to isolation and cohorting. Through a prospective observational cohort study performed in three ICUs in a French teaching hospital, Lucet et al. (2005) documented a reduction in MRSA acquisition incidence from 7% in pre-intervention period to 2.8% in post-intervention period, when screening, contact precautions, and use of alcoholic hand rub solution were introduced.

Recently, rapid methods for molecular detection of MRSA colonised patients with available results in 2 h have been developed with high sensitivity and specificity (Carroll 2008). Major limits for the wide application of molecular diagnosis for MRSA are related to the high costs and varying benefits in different studies (Table 1). A recent systematic review and meta-analysis summarized available evidence on the effect of MRSA detection by rapid screening tests on hospital-acquired MRSA infections and acquisition rate (Tacconelli et al. 2009a). Compared with culture screening, use of rapid tests was not associated with a significant decrease in MRSA acquisition rate, while a significant decreased risk for MRSA bloodstream infections, but not for MRSA surgical site infections (SSIs), was noted between wards applying rapid screening tests and those not applying screening. Two explanations might be hypothesized. Firstly, the development of SSI is strictly related to surgical prophylaxis. Second, in surgical patients undergoing emergencies surgeries results of molecular tests might not arrive before surgery. Significant heterogeneity was detected among studies, and it was partly related to the hospital settings, study design, systematic screening not performed at discharge, polymerase chain reaction (PCR) result not confirmed by conventional culture, lack of analysis of possible variation in MRSA epidemiology during the study period and absence of monitoring of compliance with decolonisation treatment or contact precautions. Conclusion of the study was that active screening for MRSA appears more important than the type of test used, and that, because of the limits and heterogeneity of available evidence, definitive recommendations cannot be made. Murthy and colleagues recently assessed the cost-effectiveness of PCR screening on admission to surgery, comparing costs and the probability of any MRSA infection across three strategies: universal screening by PCR; target screening for risk factors (prior hospitalisation or antibiotic use) combined with pre-emptive isolation and contact precautions

Table 1 Clinical studies analysing the effect of rapid molecular diagnosis for MRSA colonisation linked to contact precaution on the transmission of MRSA

Author	Study design	Setting	Intervention	Controls	Outcome
Harbarth et al. (2006a)	Interventional cohort study	MICU and SICU	PCR assay for all admissions and pre-emptive isolation	Conventional cultures	Significant reduction in MRSA infection rate in the MICU No reduction in MRSA infection rate in the SICU Significant reduction in median time to notification
Cunningham et al. (2007)	Interventional cohort study	Mixed MICU and SICU	PCR assay for all admissions	Conventional cultures	Significant reduction in MRSA transmission rate
Conterno et al. (2007)	Interventional cohort study (time-series analysis)	1200-bed tertiary-care hospital	PCR assay for high-risk patients	Conventional cultures	No decrease in the incidence of MRSA colonisation Significant reduction in median turn-around time
Jeyaratnam et al. (2008)	Cluster randomized cross-over study	Surgical, elderly care and oncology wards	PCR assay for all admissions and pre-emptive isolation of high-risk patients	Conventional cultures	No decrease in the incidence rate of MRSA transmission Significant decrease in median turn-around time and inappropriate pre-emptive isolation
Jog et al. (2008)	Interventional cohort study	Cardiac surgery unit	PCR assay for all admissions	Standard infection control alone	Significant decrease in MRSA SSI
Harbarth et al. (2008)	Interventional cohort study	Surgical wards	PCR assay for all admissions	Standard infection control alone	No decrease in nosocomial MRSA infection rate

Table 1 (continued)

Author	Study design	Setting	Intervention	Controls	Outcome
Robicsek et al. (2008)	Interventional cohort study	Three hospitals: 1, high proportion of surgery patients; 2, high proportion of LTCF residents; 3, community hospital	PCR assay for all admissions	Standard infection control alone	Significant reduction in MRSA infection rate
Keshtgar et al. (2008)	Observational cohort study	Surgical wards	PCR assay for all admissions	Standard infection control alone	Significant reduction in MRSA BSI and wound infection
Aldeyab et al. (2009)	Interventional cohort (cross-over design)	Medical, cardiology and surgical wards	PCR assay for all admissions	Conventional cultures	No reduction in MRSA acquisition rate
Richer and Wenig (2009)	Interventional cohort study	Otorinolaryngology, head and neck oncology	PCR assay for all admissions	Standard infection control alone	No reduction in MRSA SSI
Hardy et al. (2010))	Cluster randomized cross-over study	Surgical wards	PCR assay for all admissions	Conventional cultures	Significant reduction in MRSA acquisition rate

pending chromogenic agar results; and no screening. Compared to no screening, the PCR strategy resulted in higher costs but a lower infection probability and the risk factor strategy was more costly yet less effective than universal screening. Sensitivity analyses showed that on-admission prevalence of MRSA carriage predicts cost-effectiveness, suggesting that local epidemiology plays a critical role. Therefore, settings with higher prevalence of MRSA colonisation may find universal screening cost-effective (Murthy et al. 2010; Wassenberg et al. 2010).

Contact Precautions

Once MRSA positivity is detected, contact isolation should be put in place to prevent cross-transmission. Cooper et al. (2004) demonstrated that intensive concerted interventions, including isolation, can substantially reduce MRSA. In a prospective before-and-after study Mangini et al. (2007) compared the impact of contact precautions plus droplet precautions (first intervention) and contact precautions alone (second intervention) on the incidence of hospital-acquired MRSA infection in ICU and non-ICU patient-care areas. After a baseline period during which Centers for Disease Control and Prevention (CDC) standard measures were applied, combined rates of hospital-acquired MRSA infections in the medical ICU (MICU) and surgical ICU (SICU) decreased with no significant change in other ICUs. After the discontinuation of droplet precautions, the combined rate in the MICU and SICU decreased further although not significantly, this suggesting a predominant role for contact transmission of MRSA. After the implementation of contact precautions the rate decreased significantly in non-ICU areas. Although more than 100 studies have reported control of MRSA with screening linked to isolation and cohorting, two studies suggested that reporting culture results and isolating colonised patients had no impact on the prevalence of hospital-acquired MRSA. The first study assessed the effect of daily microbiological surveillance alone on the spread of *S. aureus* (Nijssen et al. 2005). During a 10-week period, surveillance cultures were performed in 158 patients. Surveillance cultures and genotyping of MRSA and MSSA isolates demonstrated the absence of cross-transmission among patients. The second study was a prospective 1-year study in the ICUs of two teaching hospitals (Cepeda et al. 2005). Admission and weekly screens were used to ascertain the incidence of MRSA colonisation. In the middle 6 months, MRSA-positive patients were neither moved to a single room nor cohort-nursed unless they were carrying other multiresistant bacteria. Patients' characteristics and MRSA acquisition rates were similar in the periods when patients were moved and not moved. The crude (unadjusted) Cox proportional hazards model showed no evidence of increased transmission during the non-move phase. However, the studies have limitations related to the small sample size and the time elapsed from admission to the results of cultures, which was up to 4 days, and would have been sufficient to allow person-to-person transmission of MRSA. Thus, current evidence suggests that active surveillance screening should be implemented to reduce hospital MRSA acquisition rate. However,

before starting active surveillance screening, laboratories should be prepared for the workload, the turnaround time for screening tests should be reduced, and systems should be put in place to monitor the effectiveness of the intervention. Another important point that should be carefully evaluated before implementation of active surveillance screening is the adverse effect of contact precautions. Accurate training of HCWs should precede the implementation of screening and contact isolation and it should not be accepted as a substitute for hand washing. In the MICU at Duke University Medical Center it was observed that HCWs were approximately half as likely to enter the rooms of patients in contact isolation (Kirkland and Weinstein 1999). In his interesting review, Millar has underlined also the ethical issue related to the pre-emptive contact precautions for patients with low risk of being colonised by MRSA (Millar 2009).

Environmental Cleaning

It has been observed that MRSA can survive for months in hospital environment (Kramer et al. 2006) and it can be isolated on clinical equipment, as well as on general surfaces especially close to patient's area, such as curtains, beds, lockers and over-bed tables (Boyce et al. 1997). Before contact precautions are implemented, MRSA carriers may have already contaminated their environment with MRSA. A recent observational study showed that 18 and 35% of MRSA colonised patients had contaminated surrounding environmental surfaces 25 h and 33 h only after admission, respectively (Chang et al. 2010). Cross-transmission between patients may occur via HCWs hands after touching contaminated environmental surfaces (Boyce et al. 1997; Dancer 2008). One study showed that 10% of HCWs fingertips were contaminated with MRSA after contact with MRSA positive patient's environment (Creamer et al. 2010).

There is evidence that cleaning removes MRSA from hospital environment with benefit for the patients, especially in epidemic settings. Rampling et al. (2001) documented an outbreak of MRSA in a urology ward, which was resistant to promotion of hand hygiene and contact isolation, while it ended only after doubling the number of ward cleaning hours. Dancer et al. (2009) have recently performed a prospective interventional crossover study to evaluate the impact of enhanced cleaning by the introduction of one additional cleaner into a surgical ward on the contamination of the clinical environment. Enhanced cleaning was associated with a 32% reduction of microbial contamination at 10 hand-touch sites, although only a small reduction in environmental MRSA was documented and authors could not demonstrate a significant reduction but only a trend in reduction of MRSA infections during the intervention period. Cleaning methods which have been demonstrated efficacious to reduce environmental MRSA include routine vacuuming and detergent-based cleaning, deep cleaning with disinfectants, and gaseous decontamination with hydrogen peroxide vapour (Dancer 2008).

Table 2 Some examples of MRSA decolonisation protocols

Protocol	Length	Reference
2% mupirocin nasal ointment	5 days	Harbarth et al. (1999)
2% mupirocin nasal ointment and 4% chlorexidine gluconate shampoo and/or bath	5–10 days	Dupeyron et al. (2006) Robicsek et al. (2009) Bode et al. (2010)
2% mupirocin nasal ointment and octenidine solution bath	5–7 days	Rohr et al. (2003)
2% mupirocin nasal ointment, 4% chlorexidine gluconate bath, and oral rifampin and thrimetoprim-sulphametoxazole	5 days	Fung et al. (2002) Simor et al. (2007)
2% mupirocin nasal ointment, 4% chlorexidine gluconate bath, and oral rifampin and doxycycline	5 days	Fung et al. (2002)
2% mupirocin nasal ointment, 4% chlorexidine gluconate bath, and oral rifampin and fusidic acid	5 days	Macfarlane et al. (2007)
2% mupirocin nasal ointment, povidone-iodine shampoo and bath, and oral vancomycin	5 days	Maraha et al. (2002)
2% mupirocin nasal ointment, and oral minocycline and rifampin	10–14 days	Darouiche et al. (1991)

MRSA Decolonisation

The majority of protocols for MRSA decolonisation include mupirocin alone or in combination with body washes and systemic therapy with one or two antibiotics such as rifampicin, doxycycline and trimethoprim-sulfamethoxazole (Table 2). Less popular protocols include tea tree oil, a popular natural antiseptic, topical gentian violet and arbekacin inhalation in patients with percutaneous endoscopic gastrostomy. The duration of the decolonisation treatment is usually 5–10 days. Decolonisation has been proven to be efficacious in reducing infections in high risk groups (Kallen et al. 2005). In a retrospective cohort study, Robicsek et al. (2009) tested the efficacy of topical decolonisation with a 5-day course of nasal mupirocin and chlorexidine gluconate bath documenting a significant risk reduction of MRSA sustained colonisation, but not of subsequent MRSA infections, although there was a trend toward delayed infection among patients receiving mupirocin. In dialysis patients the use of mupirocin reduced the rate of *S. aureus* infections by 68% (Tacconelli et al. 2003). Risk reduction was higher in peritoneal dialysis patients. In a randomized, double-blind, placebo-controlled, multicenter trial, Bode et al. (2010) assessed that rapid identification of *S. aureus* nasal carriers, followed by treatment with mupirocin nasal ointment and chlorhexidine soap before surgical procedures reduced the risk of hospital-associated *S. aureus* infection. Significant reduction of *S. aureus* infections was also observed in patients after cardiothoracic and orthopaedic surgery (Kallen et al. 2005). An additional concern on decolonisation efficacy is the need for the treatment of household members and environment. Böcher et al. (2010) investigated the prevalence of long-term carriage, the efficacy of repeated MRSA

decolonisation treatment and spread of MRSA to households, companion animals and environment of patients and HCWs. In a multivariable analysis, chronic disease and throat-carriage were associated with long-term MRSA carriage. MRSA positive households were decolonised using mupirocin and daily chlorhexidine body and hair wash for 5 days and throat-carriers also received fucidic acid combined with rifampicin or clindamycin for 7 days. The home environment was cleaned twice. No animals was colonised. Of 102 persons (19 HCWs and 83 patients) and 67 household members who agreed to participate, 10 of 16 long-term carriers and the two household contacts firstly MRSA positive were MRSA negative at the end of follow-up. None of the HCWs became positive for MRSA.

Screening and decolonisation of HCWs has been attempted for MRSA but its use remains controversial (Simpson et al. 2007). The prevalence of MRSA among professionals is related to geographical regions (Eastern Europe 1.6%, Africa 15.5%), location (ICU 4.7%, general wards 6.3%), type of HCW (nurse 8%, medical 7.4%), type of room (private cohorting 2.4%, no private/no cohorting 7.7%), and contact precautions in force (3.3%) or not applied (5.6%) (Albrich and Harbarth 2008). However, little evidence suggests that the exclusion of MRSA-positive HCWs improves the control of MRSA with the exception of hospital outbreaks. Screening might have psychological implications for professionals who test positive. Cost-effectiveness analysis for this approach in this population is also unavailable. Only staff members with colonised or infected hand lesions should be off work while receiving courses of clearance therapy (Nathwani et al. 2008).

Antibiotic Stewardship

Previous antibiotic use is frequently reported as a risk factor for MRSA isolation. Fluoroquinolones might influence oxacillin resistance by selective inhibition or killing of the more susceptible subpopulations in heteroresistant *S. aureus* (Venezia et al. 2001). Similar biological mechanisms might be hypothesized for glycopeptides and β-lactams. By eliminating MSSA these drugs might enhance the patient susceptibility to MRSA colonisation. *In vitro*, the induction of phenotypic resistance in *mec*-A positive MSSA was attempted by 24 h exposure to oxacillin and cefotaxime (Kampf et al. 2003). Schentag et al. (1998) showed that the changeover from MSSA to MRSA begins on the first hospital day, when patients are given cefazolin as surgical prophylaxis. Under selective antibiotic pressure, colonising flora change within 24–48 h. For patients remaining hospitalised, subsequent courses of third-generation cephalosporins further select and amplify the colonising MRSA population. A recent meta-analysis including 76 studies for a total of 24,230 patients documented that the risk of acquiring MRSA was increased by 1.8-fold in patients who had taken antibiotics (Tacconelli et al. 2008). Antibiotic exposure was determined in the 126 ± 184 (mean ± SD) days preceding MRSA isolation. Such risk was almost three times greater after using quinolones or glycopeptides. Significant heterogeneity was detected between studies and it was related to the length of time-

at-risk analysed, that greatly varied among studies (from 7 to 1,080 days before the infection) and to the study design. A multicentre prospective cohort study conducted in several Italian hospitals showed that 5% of patients were newly colonised by antibiotic-resistant bacteria, including MRSA, after starting antibiotic therapy. Nine percent of newly colonised patients developed an infection by the same strain over 30-day follow-up. The use of carbapenems was associated with the highest incidence of colonisation with eight new cases of MRSA colonisation for 1,000 antibiotic-days (Tacconelli et al. 2009b). The most interesting recent data come from the application of time-series analysis, although bias has been detected also with this methodology (Harbarth and Samore 2008). Using interrupted time-series analysis, Mahamat et al. (2007) prospectively evaluated the longitudinal effects of infection control interventions and antibiotic use on MRSA rates in two Scottish hospitals. Macrolides and fluoroquinolones use was independently associated with increasing number of new clinical MRSA cases. Aldeyab et al. (2008) related MRSA incidence with antibiotic usage. Retrospective analysis of a 5-year dataset showed that temporal variation in MRSA incidence followed temporal variations in the use of fluoroquinolones, third generation cephalosporins, macrolides and amoxicillin/clavulanic acid. Against this evidence, mupirocin-resistant *S. aureus* has been reported in institutions with limited use of the drug (Jones et al. 2007). In 2005, revised MRSA infection-control guidelines for hospitals from the Joint Working Party of the BSAC, Hospital Infection Society and Infection Control Nurses Association included the rational use of antibiotics and an antibiotic policy among the basic infection-control measures (Gemmell et al. 2006). A limited use of glycopeptides, cephalosporins and fluoroquinolones was strongly recommended.

Antimicrobial stewardship is a key component of a multifaceted approach to preventing emergence of antimicrobial resistance (Gould 2009). Efficient antibiotic stewardship should cover appropriate choice of empirical therapy as well as duration, dosage, side effects and costs of the drug in order to provide the best outcome for the patient and to reduce adverse effects including antimicrobial resistance (Fishman 2006; Owens 2008). Several intervention studies assessing the effect of antibiotic stewardship on hospital MRSA rates have been published. One study conducted in a department of geriatric medicine in London documented that cephalosporins restriction, the introduction of simple control measures such as emphasis on hand washing, and 7-day time limits on antibiotics, reduced the MRSA incidence from 3.9 to 1.9 per 100 hospital admissions (Stone et al. 1998). In a 2-year before and after study conducted in a surgery-trauma ICU, consisting of 1 year of non-protocol-driven antibiotic use and the following 1 year period in which a rotating antibiotic assignment was instituted, rotation was associated with a decline in the infection rates due to MRSA (Raymond et al. 2001). In an English hospital the effect of a 2-month educational intervention to discourage the use of intravenous ciprofloxacin and third-generation cephalosporins was recently assessed by observing the MRSA bacteraemia and colonization rate. With respect to the 18-month pre-intervention period, MRSA bacteraemia rate was reduced by 62.9% and MRSA colonisation rate by 38.4% (Liebowitz and Blunt 2008). A study performed in 17 adult units of a tertiary care teaching hospital in US examining the effect of ciprofloxacin

restriction on MRSA infection rate showed that while ciprofloxacin use decreased by 31.2% over the study period, the rate of MRSA infection changed only slightly overall (from 59.6 to 54.2%). Nevertheless, a correlation between ciprofloxacin use and the MRSA rate within the individual units was observed (Cook et al. 2006).

However, the best results in implementing antibiotic stewardship might be reached only with national policy and Governmental involvement. A successful experience has been recently reported from Belgium where policy guidance and federal funding for antibiotic managers was provided to all hospitals since 2002 with the organisation of on Antibiotic Policy Coordination Committee (BAPCOC). A survey performed in 2007 documented a well-developed structure of AMTs in Belgian hospitals and the broad range of services provided, including hospital antibiotic formulary (96.3%), practice guidelines for antibiotic therapy and surgical prophylaxis (91.6 and 96.3%, respectively), list of restricted antimicrobial agents (75.9%), de-escalation of therapy after a few days (63.9%), sequential intravenous/oral therapy for antibiotics with equivalent bioavailability (78.7%), dedicated antimicrobial order forms (36.1%), automatic stop of delivery (43.5%), analysis of antibiotic consumption data (96.2%), and analysis of microbial resistance data (89.8%) (Van Gastel et al. 2010).

Few reports on successful antibiotic stewardship in the community have been published. A recent systematic review of the literature included all studies evaluating strategies to reduce unnecessary antibiotic prescribing in outpatient practice. No single strategy was clearly superior, although active clinician education strategies trended toward greater effectiveness than passive strategies (Ranji et al. 2008). As an outstanding example, the French government initiated a nationwide campaign in 2001 to reduce antibiotic overuse in the community, especially for viral respiratory infection during the influenza season. After a 5-year campaign a 26% reduction in antibiotic prescriptions was achieved (Sabuncu et al. 2009).

Guidelines from the Society of Hospital Epidemiologists of America (SHEA) and the Infectious Diseases Society of America (IDSA) strongly support the wide diffusion of antibiotic stewardship programs in healthcare settings (Dellit et al. 2007). In Europe, the ABS (AntiBiotic Strategies) International was instituted by the EU Commission in September 2005 to implement antibiotics strategies for appropriate use of antibiotics in hospitals in member states. However, as stated earlier, available evidence does not strongly support the cost-effectiveness of antibiotic stewardship programs. In a questionnaire, to 127 hospitals participating in the antibiotic resistance surveillance and control in the Mediterranean region project (ARMed), four major areas were explored: presence of infrastructures and personnel; ability to put patients in contact precautions; compliance of staff to hand hygiene programs; and antibiotic stewardship. Answers showed that application of antibiotic stewardship does not necessarily guarantee low level of antimicrobial resistance (Borg et al. 2009). The only differences identified among countries were in terms of bed occupancy and isolation facilities. Hospitals with frequent episodes of overcrowding had the highest MRSA proportion.

Even in a clinical setting with low economic resources, Cheng et al. (2009) were able to implement an antibiotic stewardship programme focused on broad-spectrum intravenous antibiotics including new guidelines developed by the antimicrobial

stewardship team and an immediate concurrent feedback on clinicians prescriptions. The intervention reduced antibiotics consumption from 73.06 DDDs at baseline to 64.01 per 1,000 patient bed-day-occupancy in the post-intervention period. However, the use of meropenem increased markedly (more than 50%). Reviewing the trend of antibiotic susceptibility patterns, piperacillin-tazobactam and ceftazidime-resistant *Klebsiella pneumoniae* decreased from 22 to 11% and 16 to 12%, respectively, while ceftazidime-resistant *Escherichia coli* and antimicrobial-resistant *Acinetobacter baumannii* isolates increased during the study period.

This last example clearly shows the potential limit of antibiotic stewardship. In our opinion, antibiotic stewardship has to be a cornerstone in the fight in every hospital worldwide to decrease antibiotic-resistance. More important, the problem of resistance in nosocomial infections is definitively not limited to methicillin resistance in *S. aureus* and this should be carefully considered when planning infection control measures in a hospital.

As described above, numerous studies have shown that it is possible to change antibiotic prescription attitudes in hospital, at different ecological, cultural and economic levels, and this has a strong impact on the rate of infections and colonisations by MRSA. On the other hand, the major risk we foresee for the implementation of antibiotic stewardship is the lack of serious evaluation of complexity of the intervention, which should include the best strategy adapted to the local ecology and strict quality indicators, previously defined. The attractive temptation to implement an "homemade" antibiotic stewardship programme that does not take into account potential adverse effects is easy to forecast and might have dramatic consequences. Major negative effects could be the increase of antibiotic-resistance in microorganisms other than the target bacteria of the programme (for example *Clostridium difficile* when reducing MRSA). A poorly designed antimicrobial stewardship programme might also increase costs related to the unrestricted drugs and their collateral effects (such as renal failure for increased aminoglycosides use). Therefore, we strongly support the elaboration of an antibiotic stewardship intervention by a panel of experts including microbiologists, infectious diseases specialists, pharmacists, economists and Public Health officers.

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The Role of Antibiotic Policies in Controlling VRE

Abhijit M. Bal

Abstract Antibiotic resistance is an emerging problem. Vancomycin resistant enterococci pose a significant problem in many areas of the world. The emergence of VRE has been linked to the use of glycopeptides both in environmental as well as clinical setting. Transmission of VRE between patients is associated with poor compliance with infection control policies. Antibiotic formulary intervention has shown to be of some benefit in reducing the rate of acquisition of VRE within the health care setting. This review focuses on the extent to which antibiotic policies help control the growing trend of VRE and suggests some interventions that could be potentially rewarding.

Keywords Antibiotic stewardship • Vancomycin • VRE • Teicoplanin • Daptomycin • Linezolid

Introduction

The growing problem of antibiotic resistance has been established beyond doubt. Resistance to antibiotics has involved almost all available antibiotics and all species of bacteria pathogenic to man. Most recently, the emerging resistance in Gram-negative Enterobacteriaceae to carbapenems and several other antibiotic classes has been highlighted in an investigation carried out in India and the UK. These strains produce the New Delhi metallo β-lactamase 1 enzyme that confers resistance to several antibiotic classes. Only colistin and to some extent tigecycline appear to be active against these strains (Kumarasamy et al. 2010). The trend of antibiotic resistance in Gram-positive bacteria is by no means less important. Infection with Meticillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) is a reality that clinicians face in their day to day practice all over the world. More ominously, lack of susceptibility to newer agents such as linezolid and daptomycin

A. M. Bal (✉)
Consultant Microbiologist and Honorary Clinical Senior Lecturer, Crosshouse Hospital, NHS Ayrshire and Arran, Lister Street, Kilmarnock KA2 0BE, Scotland, UK
e-mail: abhijit.bal@nhs.net

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_7, © Springer Science+Business Media, LLC 2011

that act exclusively on Gram-positive organisms has already been reported (Lopez and Jhaveri 2009; Hidron et al. 2008).

It is generally well appreciated that antibiotic resistance can be tackled at various levels and an increase in overall antibiotic consumption is associated with growing resistance. Reducing the consumption of antibiotics decreases the selection pressure on microbes. Sound infection control protocols aim to reduce the transmission of resistant bacteria between patients and effective treatment strategies help reduce the burden of resistant organisms in an individual patient thereby curing the patient as well as eliminating the opportunities for transmission. It is important to emphasize however that there is no one strategy for reducing antibiotic resistance. The optimal strategy depends upon various factors such as the nature of resistance, the dynamics of antibiotic use, the institutional setting, and the awareness of the problem amongst the health care workers.

VRE are unique in some sense because the link between use of antibiotics and selection of resistant strains is less straight-forward when compared to other multi-resistant organisms. In other words, patients with VRE do not always have a history of direct exposure to vancomycin. Rather, they often get colonized as a result of transmission of strains from another source. Antibiotics readily create an ideal environment for a transmitted strain to establish itself. For example, broad-spectrum cephalosporins such as ceftriaxone alter the gut flora and this allows enterococci to colonize the gut in absence of pressure from competing microbes. Cephalosporins are inactive against enterococci. Thus, both antibiotic pressure and lack of infection control play an important role but at very different levels. VRE colonisation as a result of antibiotic misuse is perhaps more indirect.

The Enterococci

Briefly, enterococci are Gram-positive cocci that are colonisers of the human gut. Enterococci are generally of lower virulence when compared to other Gram-positive cocci such as *Streptococcus pyogenes* but this does not in any manner compromise their tenacity. These organisms can cause a wide range of infections often as part of polymicrobial sepsis (e.g. complicated intra-abdominal abscesses). They also cause infective endocarditis. Medical management of enterococcal endocarditis has a high failure rate. The two main species of enterococci associated with human infection include *E. faecalis* and *E. faecium*. Other species that are clinically encountered include *E. durans*, *E. avium*, *E. gallinarum*, and *E. casseliflavus*. The latter is often resistant to vancomycin. Surveillance reports indicate that upto 40% of *E. faecium* invasive (isolated from bloodstream) strains in the United Kingdom are resistant to vancomycin (Brown et al. 2008). More ominously, the VRE strains often carry the *vanA* gene making them resistant to teicoplanin as well. In contrast, strains belonging to the vanB phenotype are resistant to vancomycin but have low-level resistance to teicoplanin. Other clinically and epidemiologically relevant enterococcal phenotypes also exist including vanC, vanD, vanE, vanG, and vanL (Werner et al.

2008). Vancomycin resistant strains are more likely to infect patients with severe illness such as patients with acute myeloid leukaemia (Worth et al. 2007). Spread of VRE is usually polyclonal implying the easy transfer of mobile genetic elements into various recipient clones (Kawalec et al. 2007). Clearly, steps must be taken in order to reduce the prevalence of vancomycin resistance. But generally, VRE has attracted lesser attention compared to MRSA. Thus, in several Scandinavian countries such as Denmark and Norway, the regulations surrounding MRSA screening is far more stringent than for VRE which is not perceived as a major problem to the extent that MRSA is. In countries such as the United Kingdom, invasive infections with VRE are a significant cause for concern particularly in large teaching hospitals (Werner et al. 2008).

How Does Antibiotic Misuse Contribute to Emerging Resistance?

Unrestricted and uncontrolled antibiotic use contributes to the development of resistance in two fundamental ways. The first is induction of mutation. Thus, bacteria exposed to antibiotics may thrive by developing mutations that make them resistant to antibiotics provided the mutation is not incompatible with survival. The rapidity of mutation depends upon both, the species of bacteria and the class of antibiotic. For example, rifampicin resistance as a result of mutation develops rather quickly in *S. aureus*. The second kind of resistance becomes apparent when bacteria with some sort of existing resistance mechanism get selected as a result of antibiotic use. As discussed above, VRE may get selected because of inappropriate use of broad-spectrum antibiotics such as third-generation cephalosporins. It then implies that better control of antibiotics would help reduce the problem of VRE.

Antibiotic Policies and VRE

It has been suggested that half of all antibiotic prescriptions are unnecessary or in other words, the antibiotics are used when not using them would cause little harm. According to Dryden and colleagues, antibiotic stewardship "promotes the use of the right antibiotic, at the right dose, route and duration, for the right bacterial infection at the right time". Continuing education, better diagnostic methods and prescribing regulations are some of the key factors that help attain the goal of eliminating inappropriate prescribing (Dryden et al. 2009). If inappropriate antibiotic use selects for multi-resistant organisms, then it follows that reduced consumption or control on prescriptions should reverse the trend. In practice however, the equation is less straight-forward. Gould noted that the evidence that establishes a direct relationship between antibiotic policies and rate of resistance was far from robust (Gould 2002). Studies that have tried to correlate the antibiotic guidelines

to rate of resistance have suffered from several drawbacks because the presence of a hospital-wide guideline is no indication of whether the guidance is implemented and complied with. In this context, Larson and colleagues draw our attention to the importance of the wider organizational and administrative factors in tackling the problem of resistance (Larson et al. 2007).

Antibiotic consumption outside the health care setting must also be looked into particularly in the context of VRE. The association of avoparcin (a glycopeptide) in animal feed with VRE is well known (Bates 1997) and as a result, this agent was banned from use in farming in 1997 (Cookson et al. 2006). VRE are more likely to be detected in pigs and poultry birds which were fed on diet containing this glycopeptide. Other antibiotics such as macrolides and streptogramins have also been implicated as drivers of VRE in animals and the restriction on their use has caused a reduction in the prevalence of VRE because genes that encode for macrolide and glycopeptide resistance may be genetically linked (Aarestrup et al. 2001). There is some evidence that the prevalence of VRE in the community has also deceased following the European Union ban on some of these agents (Klare et al. 1999). This does not explain the significant numbers of VRE in America where avoparcin was never used (Bonten et al. 2001). The epidemiological link between vancomycin use and high prevalence of VRE might be an alternative explanation in countries outside Europe. Reduction of vancomycin use has been shown to reduce the prevalence of VRE (Richardson et al. 2000; Anglim et al. 1997). Shaikh and colleagues demonstrated a reduction in VRE bloodstream infections from 0.338 to 0.181 per 1,000 patient days ($P=0.027$) by reducing the empiric use of vancomycin from 416 to 208 gms/1,000 patient days ($P<0.001$). The vancomycin restriction program limited the use of this agent to four specific situations and required the clinician to fill a vancomycin order form (Shaikh et al. 2002).

Within hospital setting, it is recommended that institutions develop a strong antibiotic policy particularly so if there were issues such as emergence and spread of VRE and other resistant microbes. However, it should be appreciated that good antibiotic policy must go hand in hand with other effective measures such as hand hygiene, isolation of patients and environmental cleaning. Measures that are taken to control the spread of VRE depend upon the extent of the problem and nature of the spread. An outbreak of VRE in a critical setting is best controlled by strict adherence to infection control measure such as source isolation and hand washing rather than by antibiotic policies in the immediate period following the recognition of the outbreak. On the other hand, it is imperative that the antibiotic policies be reviewed if the nature of spread is slow and over a period of months or years and the goal is to tackle the residual endemicity (although infection control measures would still need to be implemented). An outbreak in the intensive care unit and the dialysis unit of the Royal Perth Hospital, Australia, was controlled with the help of enhanced infection control measures (including screening of patients and ward contacts, cohorting, environmental screening, and electronic flagging of medical records). The investigators recognized that a major contributing factor that was responsible for the outbreak was high antibiotic consumption in the hospital and this led to the introduction of an antibiotic stewardship program to prevent future outbreaks (Pearman

2006). Much in the same way, surveillance cultures, cohorting and education failed to reduce colonisation of VRE over 4 years (2005–2008) even in a comparatively small hospital with 150 beds in Sao Paulo, Brazil. Indeed, antibiotic stewardship was not one of the several measures instituted by the infection control team at the hospital (Pereira et al. 2010). Larger hospitals, which are likely to be more difficult to manage in terms of sheer size but are also likely to possess better resources, have also struggled to eradicate VRE following an infection control program that did not include antibiotic stewardship. Kurup and colleagues in Singapore General Hospital managed to reduce the prevalence of colonisation of VRE from 11.4 to 4.2% in a short span of a few weeks following an outbreak. However, a certain level of endemicity continued to prevail possibly due to the fact that antibiotic stewardship was not a strong component in the strategy. This is extremely important to attain the long term objective of elimination of VRE although antibiotic stewardship is unlikely to be effective on its own in a short period of time. Although the investigators did educate the staff about reducing the use of antibiotics as far as the use of vancomycin was concerned, their data suggests only a modest level of compliance (Kurup et al. 2008). Beaumont Hospital in Dublin achieved a reduction in bloodstream VRE infections from 0.78 per 10,000 bed days in 2005 to 0.46 per 10,000 bed days in 2008. The hand hygiene compliance was 28% in 2005 compared to 69% in 2008. The hospital had also employed an antibiotic pharmacist in order to implement a comprehensive antibiotic stewardship program (Morris-Downes et al. 2010).

Is There Evidence that Specific Antibiotic Interventions Reduce VRE?

In order to implement effective antibiotic policies that would be expected to reduce the incidence of VRE colonisation or infection, we must first tailor the antibiotic guideline in a way that reduces the selection pressure in favour of enterococci. Animal models have demonstrated that antibiotics such as piperacillin-tazobactam that are active against enterococci reduce the chances of colonisation with these strains. Thus, while ticarcillin-clavulanic acid and ceftriaxone promote VRE colonisation (both are poorly active against enterococci), piperacillin-tazobactam inhibits colonisation (Donskey et al. 2000). These findings have been replicated in studies involving humans. Following a formulary switch from ticarcillin-clavulanic to piperacillin-tazobactam, Winston and colleagues demonstrated a reduction in acquisition of VRE from 11.5 to 7.6% and a reduced rate of isolation of VRE from cultures other than stool from 39 (0.58/1,000 bed days) in the period prior to the switch to 27 (0.33/1,000 bed days) following the switch (Winston et al. 2004). Quale and colleagues demonstrated that restriction of third generation cephalosporins and vancomycin reduced the prevalence of faecal colonisation of VRE from 47 to 15% (Quale et al. 1996). Bradley and colleagues reported a reduction in acquisition of VRE from 57% to 19% by making the switch from ceftazidime to piperacillin-tazobactam for empirical therapy of febrile neutropenia. When ceftazidime was reintroduced, the

rate of acquisition rose to 36%. At the time of the initial switch to piperacillin-tazobactam, an intensive hand hygiene program was also introduced and the educational program was continued when ceftazidime was reintroduced. Clinically significant infections were encountered only during the ceftazidime phases. Compliance with the policy in all three phases was well documented. Even though the study does not appear to be suitably blinded, the rise in the acquisition of VRE following the reintroduction of ceftazidime at a time when the education and awareness program was continued offers some evidence for the association between third generation cephalosporins and VRE and argues favourably for the case of switching to agents that do not promote acquisition of multi-resistant pathogens (Bradley et al. 1999). In contrast, Lautenbach and co-workers found little benefit despite a significant reduction in the use of third generation cephalosporins (Lautenbach et al. 2003). One possible explanation for the discrepant result is the aggressive education program that was implemented by Bradley and colleagues. Although it is difficult to define the exact role of these individual components, it does appear that the best results are obtained when infection control program is implemented hand in hand with antibiotic stewardship program. However, one common theme in Quale's (Quale et al. 1996) as well as Lautenbach's study (Lautenbach et al. 2003) is the link between clindamycin use and VRE. It is well known that the third generation cephalosporins are modestly active against Gram-positive cocci and clindamycin, due to its superior activity against many of these organisms other than enterococci, may provide an excellent habitat for the enterococci to flourish. A group of Polish investigators also studied the efficacy of antibiotic formulary interventions coupled with specific infection control measures in reducing the incidence of VRE colonisation and infection. Significant reduction in the use of aminoglycosides, carbapenems, cephalosporins, and cotrimoxazole led to the control of the outbreak of VRE in the tertiary haematology centre of the hospital (Ozorowski et al. 2009).

Organizational Issues

It is thus apparent that the war against nosocomial VRE infections can be won only by a multi-disciplinary approach that ties the interests of the hospital infection control program and antibiotic stewardship together. At a broader level, organizations would need to develop capacities which link hospitals with public health authorities. Governments will ultimately need to decide the extent of the measures that need to be undertaken to tackle the growing threat of antibiotic resistance. For example, an MRSA screening program was initiated in three hospitals in Scotland in order to study the efficacy of this intervention in controlling MRSA infections (Reilly et al. 2010). Mandatory surveillance for VRE has been proposed in the United States of America although the Society for Healthcare Epidemiology of America (SHEA) and Association of Professionals in Infection Control and Epidemiology (APIC) Task Force did not support the proposed legislation (Weber et al. 2007). In any case, a very high compliance (almost approaching 100%) is necessary before

surveillance can be effective in the control of VRE (McGowan 2004). Even in a medium sized hospital, surveillance cultures were found to cost over $ 250,000 over a 2-year period (Muto et al. 2002). Thus, important drawbacks of some of the aggressive infection control methods are clearly evident. While dramatic reduction in transmission of VRE has been achieved in many situations with the help of targeted measures, eradication of VRE has been nearly impossible in most hospitals as discussed previously. Mathematical modelling predicts that a baseline VRE prevalence of 12% would be quickly achieved in haemodialysis units and the one factor that would impact favourably on this high prevalence would be the number of patients per health care worker. A reduced patient to health care worker ratio of 1:1 would bring down the prevalence to 3% (D'Agata et al. 2002).

Conclusion

Notwithstanding the disagreements on various issues, it is clear that combating antibiotic resistance globally would need well coordinated measures. Antibiotic policies are crucial but they cannot be effective without active infection control program. A hospital with a strong infection control program without an antibiotic stewardship component would tackle transmission of multi-resistant organisms such as VRE but would not prevent individual patients from getting colonised or infected with resistant microbes. On the other hand, strong antibiotic stewardship would be expected to control the menace of multi-resistant organism but in absence of an infection control program, transmission of organisms (even if not multiply resistant) would be easy and would adversely affect patient care. It thus becomes obvious that we need a more comprehensive program which brings the two components closer in an "equal partnership" (Gould 2009; Vonberg et al. 2008). One notable area of future research is antibiotic heterogeneity (antibiotic cycling or antibiotic mixing) which is supported by mathematical modelling (Bonhoeffer et al. 1997) but has not yet had the practical success to fulfil the theoretical aspirations. Whether heterogeneity reduces resistance in enterococci is unknown at this point.

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The Control of ESBL-Producing Bacteria

Peter M. Hawkey

Abstract Infections caused by Extended Spectrum Beta Lactamase (ESBL) producing Gram-negative bacteria have emerged over the last twenty years as a major worldwide problem for treatment. Initially the ESBL-enzymes of the TEM and SHV type were identified, these did not reach high rates and were most common in *Klebsiella* spp rather than *E.coli*. ESBLs of the CTX-M type have become the most common and widespread type particularly in community strains of *E.coli*. Faecal colonisation in both infected patients and asymptomatic carriers is the most important source so successful infection control measures are directed at reducing spread from that source. Antibiotic restriction has been demonstrated to control the rate of ESBLs, reduction in third generation cephalosporins and quinolones having the greatest impact when combined with source control/hand washing as infection control interventions. Substitution of these selective agents by piperacillin/tazobactam and carbapenems results in ESBL-reduction particularly if combined with use of a diversity of other narrow spectrum agents. There are widely differing rates of ESBLs around the world which broadly correlates with the overall hospital/community prescription, agricultural and over the counter usage of quinolones and cephalosporins. Application of antibiotic stewardship is an important control measure when supported by control of the sources and routes of spread of ESBL-producing *Enterobacteriaceae*.

Keywords Antibiotic resistance • ESBL • CTXM • UTI • Gut carriage • Cephalosporins

Introduction

Extended spectrum or third generation cephalosporins e.g. cefotaxime, ceftazidime, ceftriaxone (3GCs) were introduced into clinical use in the early 1980s to provide effective therapy largely for nosocomial infections caused by multi-resistant and

P. M. Hawkey (✉)
School of Immunology and Infection, University of Birmingham, Edgbaston,
B15 2TT, Birmingham, UK
e-mail: peter.hawkey@heartofengland.nhs.uk

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_8, © Springer Science+Business Media, LLC 2011

especially gentamicin resistant *Enterobacteriaceae,*particularly *Klebsiella* spp, *Enterobacter* spp and *Pseudomonas aeruginosa*. Resistance appeared initially in bacteria such as *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens* and *Pseudomonas aeruginosa* that was caused by mutation in genes controlling expression of β-lactamase production leading to the overproduction of the chromosomal AmpC (also known as Ambler class C) β-lactamase, giving resistance to both 7-α-methoxy- and oxyimino-cephalosporins as well as monobactams (Sanders 1987). In 1988 the first description of a plasmid-mediated AmpC β-lactamase (MIR-1, 90% identical to the chromosomal gene of *E. cloacae*) was published (Papanicolaou et al. 1990), followed by many other examples (Philippon et al. 2002). Plasmid mediated resistance was also noted arising from a different evolutionary route very soon after the use of 3GCs, initially in Germany in 1983 (Knothe et al. 1983). The resistance was mediated by a single nucleic acid variant of the SHV-1 Ambler class A β-lactamase named SHV-2. Shortly after, a similar variant of the common and very widely distributed TEM-1/2 was reported from France in 1984, originally called CTX-1 but later correctly re-named TEM-3 (Sirot et al. 1987). The term extended spectrum β-lactamases was coined by Philippon and colleagues in 1989 to describe these β-lactamases (Philippon et al. 1989). The plasmid-mediated AmpC β-lactamases (Philippon et al. 2002) as well as both metallo- β-lactamase such as VIM, IMP etc and Ambler class A KPC carbapenemases are all capable of hydrolysing 3GCs resulting in a proposal to broaden the definition of ESBL to include these β-lactamases (Giske et al. 2009). This wider definition has not been widely adopted and in this chapter the following definition will be used: ESBLs are β-lactamases generally acquired rather than inherent to a bacterial species, that confer resistance to oxyimino-cephalosporins but not carbapenems. Some are mutant derivatives of well established plasmid mediated β-lactamases (e.g. TEM/SHV) which in their un-mutated form are not able to degrade oxyimino-cephalosporins. Others (e.g. CTX-M types) have been mobilized on plasmids from chromosomal genes in environmental/opportunistic bacteria.

Surprisingly, despite the heavy selection pressure extensive worldwide use of 3GCs imposed, SHV and TEM derived ESBLs did not become widely distributed outside of *Klebsiella* spp. associated with nosocomial infection (particularly ICU) (Paterson and Bonomo 2005). However, in some parts of the world the prevalence of the ESBL-phenotype in the 1990s in the very limited surveys available, was very high (20–40%) particularly in India (Ensor et al. 2006) and China (Munday et al. 2004b). In a review of ESBLs in 1995 amongst rare and unusual ESBLs there was a brief mention of two class A ESBLs: MEN-1 (now CTX-M-2) and CTX-M-1, which were not closely related in DNA sequence to TEM/SHV and were then thought to be derived from the chromosomal K1 β-lactamase of *K. oxytoca* (Sirot 1995). During the 1990s CTX-M-2 was noted to be the most common ESBL-genotype in Argentina (Paterson and Bonomo 2005). The description of CTX-M-14 from isolates identified in Guangzhou, China (Chanawong et al. 2002) preceded its recognition as the most common ESBL-genotype in the Far East (Munday et al. 2004b). CTX-M-14 together with CTX-M15, which is both the most common ESBL worldwide and

the only CTX-M genotype found in the Indian sub continent (Ensor et al. 2006), are now the most common and widely distributed genotypes of ESBLs in the world (Hawkey and Jones 2009). Both genotypes are now becoming more common in the USA where previously CTX-M was thought to be rare (Castanheira et al. 2008).

Epidemiology

The epidemiology of nosocomial infection by *Klebsiella* ssp. was elucidated in the late 1970s when gentamicin resistant strains became widespread in hospitals (Casewell et al. 1977). Gastro-intestinal colonisation was identified as an important source for cross-infection often via hands and simple procedures involving touch contact with an un-colonised patient. Various moist environmental sources such as soaps, cloths, mops, baths/basins and equipment have been described as important sources allowing persistence and spread of clones of *Klebsiella* ssp. in the hospital ward. Unsurprisingly this same pattern of epidemiology is seen with ESBL-producing *Klebsiella* ssp.

The epidemiology of *E. coli* producing CTX-M β-lactamases is somewhat different to the TEM/SHV ESBL-producing *Klebsiella* ssp. A Spanish study showed that a significant proportion of patients with ESBL-producing *E. coli* bacteremia (51%) were either strictly community acquired or health-care associated i.e. not directly acquired as a result of admission to hospital (Rodriguez-Bano et al. 2006). Very low rates (≤20%) of *E. coli* for inter-patient transmission were observed in a study of an ICU for 3 years supporting the important role of importation ESBL *E. coli* strains (Harris et al. 2007a). The importance of movement of strains from the community was further explored in a study of faecal colonisation in two cohorts of patients. In one cohort of 241 patients screened at admission, 26 patients were found with ESBL-producing *Enterobacteriaceae* on admission. The second cohort of 80 patients with bacteremia within 48 h of admission identified 11 patients with ESBL of whom 8 were health care associated (Ben-Ami et al. 2006). Using a retrospective case control study a further 38 ESBL-bacteremia patients were identified (31 health care associated) and predictors of ESBL-production were identified as male sex and nursing home residence. The authors drew attention to the challenge that this influx of ESBL makes to infection control procedures and antibiotic stewardship within the hospital (Ben-Ami et al. 2006). This occurrence of CTX-M ESBL-genes in the commensal flora of the general population has been confirmed in surveys in the UK (Munday et al. 2004a) and Spain (Valverde et al. 2004) where both CTX-M-15 and 14/9 were the most common genotypes. The dominance of CTX-M-15 in particular is thought to be due at least in part to the success of the internationally dispersed clone 025b: H4-ST131 (Nicolas-Chanoine et al. 2008). This clone was identified as a minority (22%) of *E. coli* isolates in a recent Spanish study but with a very strong association with patients resident in long-term care homes (Blanco et al. 2009). This group also noted that all the ST131 isolates were resistant to both ciprofloxacin

and co-trimoxazole, oral antibiotics frequently used in the community. This high frequency of cross-resistance to unrelated agents has frequently been noted in other studies and represents a major challenge to the control of ESBLs by restriction of antibiotic use, which will be considered in the next sections.

Direct Selection of ESBL-Producing Bacteria by 3GCs and Other Agents

The prevalence of ESBL-producing bacteria (particularly *Klebsiella* spp.) in a hospital setting is influenced by the number of source patients, rates of cross-infection between them and the antibiotic selective pressure. ESBL-producing bacteria are not only present in hospitals from endemic nosocomial sources but are introduced into the hospital from other health care facilities (particularly high rates occur in care of the elderly homes (Rooney et al. 2009)) but also from individuals coming from the community (Ben-Ami et al. 2006). The community setting frequently involves *E. coli* (see epidemiology above) and the influence of human use of antibiotics providing selection is much less significant (the intensity of antibiotic use in general practice is much lower than that in hospitals). Much more complicated transmission and selection networks involving many different factors occur in the general environment (soil, water, animals, etc.) which in turn influence the frequency and distribution of ESBL-producing *Enterobacteriaceae* (Gaze et al. 2008). These include the rate of movement of *Enterobacteriaceae* between water, food animals and the human population, the relative fitness of different bacterial strains and non antibiotic compounds that are selective agents such as quaternary ammonium compounds (Gaze et al. 2005).

Third Generation Cephalosporins

Within the hospital setting there are many studies demonstrating a strong correlation between the heavy or increased use of 3GCs and the occurrence of ESBLs in *Klebsiella* and to a lesser extent *E. coli* (Asensio et al. 2000; Du et al. 2002; Lautenbach et al. 2001; Meyer et al. 1993; Paterson et al. 2004; Pessoa-Silva et al. 2003; Rice et al. 1990, 1996a). It has been observed that there is substantial variation in such studies in categorising prior antibiotic use as either specific agent; spectrum of activity or a combination of both (MacAdam et al. 2006). The group modelled published data on ESBL-producing *K. pneumoniae* using the two different categorisations which led to markedly different conclusions on the association of the use of particular antibiotics with resistance. The same group showed how important the definition of "exposure" is i.e., at least one dose given versus 24/48 h usage in altering antibiotic exposure and resistance associations (Hyle et al. 2007). However, in studies which are carefully controlled they still provide strong evidence for

selection. One of the earliest studies providing compelling evidence for selection was that of Rice and colleagues (Rice et al. 1996). They demonstrated a statistically significant ($p=0.002$) association with the amount of ceftazidime prescribed on a ward at the Cleveland VA Medical Centre between January and December 1997 and the prevalence of ESBL *K. pneumoniae*. A much larger and longer study (9564 isolates, 9 years) of ESBL *K. pneumoniae* at a Czech University hospital showed a highly significant ($p=<0.05$) association with rising 3GC consumption and the prevalence of *K. pneumoniae* (8–18%) (Urbanek et al. 2007). In a study of risk factors for bacteraemia caused by ESBL-producing *E. coli*/*K. pneumoniae* in China only prior treatment with 3GCs was identified as an independent risk factor (OR 4.15, $p=0.008$) (Du et al. 2002). The most comprehensive and rigorous multicentre case control study recently published studied risk factors and prognosis in community onset bloodstream infections (COBSI) caused by ESBL-producing bacteria and is the only such comprehensive study of community disease (Rodriguez-Bano et al. 2010). Identifying the appropriate design of study to investigate risk factors for infections due to antibiotic resistant bacteria is difficult. The identification of risk factors in patients infected with a specific resistant bacterium should use control group patients drawn from those with infections caused by susceptible bacteria. This type of design may overestimate the importance of prior antimicrobial use as patients who had received antimicrobials are likely to be underrepresented in the control population (Harris et al. 2001). If control patients are chosen from all patients at risk this is avoided, however some of the identified risk factors might then be surprisingly associated with the risk of developing an infection caused by a susceptible bacterium. These limitations can be overcome by using a double case-control design (patients with resistant and susceptible bacteria make up the two case groups for comparison with the control) or as was used in the Rodriguez-Bano study a case-control-control design where patients with community onset sepsis and community onset bacteraemia due to *E. coli* are matched with COBSI patients with ESBL-producing *E. coli*. Although matched for hospital and time period other variables are not matched such as age, sex, severity of co-morbid conditions which might be risk factors themselves. Age, sex, cirrhosis of the liver and obstructive disease of the urinary tract were risk factors only in the sepsis population (Rodriguez-Bano et al. 2010), these would be non-specifically associated with *E. coli* COBSI. Health care associations (particularly care home residency), urinary catheter and previous antimicrobial use were risk factors in both populations demonstrating a true association with ESBL-producing *E. coli.* Prior use of cephalosporins was only significantly associated with the non ESBL COBSI group (this is a community study so patients were not exposed to 3GCS) whereas fluoroquinolones were strongly associated with both groups signifying their key role in selecting ESBL *E. coli* (Rodriguez-Bano et al. 2010). The selective effect of 3GCs for ESBLs can be demonstrated across different hospitals in a geographic arena. A study of 15 hospitals in Brooklyn, NY demonstrated the selection and spread of ESBLs producing *K. pneumoniae* and using multiple linear regression a strong association with the use of a cephalosporin plus aztreonam ($P=0.05$) was shown, whereas no relationship with the use of any other antibiotic emerged (Saurina et al. 2000).

In a large prospective observational international study of bacteraemia caused by *K. pneumoniae* a subset of 108/322 episodes were caused by ESBL-producing strains. When compounding variables were adjusted for, a significant association (OR 3.9, CI: 1.1–13.8) with prior administration of a β-lactam antibiotic containing an oxyimino group (cefuroxime, cefotaxime, cefixime, ceftazidime or aztreonam) was found (Paterson et al. 2004). The selective effect of 3GCS is not confined to adults as analysis using a multiple-logistic regression model of an outbreak of ESBL-producing *K. pneumoniae* in a paediatric ICU in Madrid demonstrated a strong association with prior exposure to 3GCs and aminoglycosides (OR 31,2 CI 3.3–298) (Asensio et al. 2000).

The strong selective pressure that 3GCs impose for ESBL-producing bacteria is further illustrated by the emergence of ESBL-producing *Enterobacteriaceae* during the administration of cefotaxime as part of selective diagnostic tract decontamination (SDD) regimens. An outbreak of nosocomial infection in an ICU of ESBL-producing *E. coli* and *K. pneumoniae* (all producing CTX-M-15 and SHV-5) was driven by the use of cefotaxime (Al Naimeri et al. 2006). A recently published national, prospective cluster randomised trial in the Netherlands of SDD in the ICU demonstrated a 13% reduction in 28 days mortality at the expense of a highly significant increase in the incidence of ESBL-producing *Enterobacteriaceae* both in faecal colonisation and VAP (Oostdijk et al. 2010). Finally the administration of ceftiofur and cefquinome to pigs pre-colonised with CTX-M-1 producing *E. coli* was found to be statistically significantly better than amoxicillin at both selecting faecal carriage and maintaining carriage post antibiotic withdrawal (Cavaco et al. 2008).

Fluoroquinolones

A highly significant observation linking ciprofloxacin resistance with ESBL production was made in 2000 when an International study of bacteraemia caused by *K. pneumoniae* noted that 25/452 episodes were caused by ciprofloxacin resistant strains of which 60% were ESBL producers (Paterson et al. 2000a). A variety of explanations were proffered but most significantly a potential linkage through the very first description of plasmid mediated quinolone resistance (Martinez-Martinez et al. 1998) was suggested. Although why the low-level resistance that was conferred by the plasmid and the fact that most clinical strains of ciprofloxacin resistant ESBL-producing bacteria have high level resistance caused by mutations in *gyr A*located on the bacterial chromosome was not clear. Subsequently the *qnr* and *aac-6′-I-cr* genes mediating low-level quinolone resistance have been shown to be widely distributed on ESBL-encoding plasmids (Cattoir and Nordmann 2009). It is currently thought that the strong association of high level quinolone resistance with ESBL production (Ensor et al. 2006) is due to the plasmid mediated genes enabling strains to survive low levels of quinolones favouring the selection of gyr A mutations followed by clonal expansion (Hawkey and Jones 2009). Two important recently published studies (Wener et al. 2010; Rodriguez-Bano et al. 2010) have

shown clear statistically significant associations with the prior administration of fluoroquinolones and colonisation/infection by ESBL-producing *Enterobacteriaceae*.

Other Antimicrobials

Despite early studies demonstrating a clear value to substituting β-lactam/β-lactamase inhibitors (notably piperacillin/tazobactam) to reduce selection of ESBL (Patterson et al. 2000b; Rice et al. 1996) more recent studies have shown a statistically significant association with colonisation at admission and piperacillin-tazobactam and vancomycin administration (Harris et al. 2007b) and β-lactamase inhibitor combinations as a class (Wener et al. 2010). This effect may be due to emergence of CTX-M-15 producing ESBL strains worldwide which frequently produce OXA-1 β-lactamase which confers resistance to β-lactamase inhibitor combinations (Hawkey and Jones 2009).

Role of Control of Antimicrobial Prescribing in Reducing the Occurrence of ESBL-Producing *Enterobacteriaceae*

As summarised above, there is an extensive body of literature supporting a strong selective effect particularly for third generation cephalosporins and the occurrence of ESBLs. Logic suggests that the removal or reduction in the use of 3GCs should lead to a reduction in the occurrence of ESBLs and there are a number of studies which support this hypothesis. However, there are studies where a reduction was not seen. The most notable clinical situation in which this occurs was first reported by Rice and colleagues (Rice et al. 1990), who dealt with an outbreak of ESBL-producing *Klebsiella pneumoniae* in a chronic care facility by substantially reducing the usage of ceftazidime. The authors did not delineate the extent of their success in restricting the drug and this may well have been a major factor in contributing to the persistence of the ESBL-producing *K. pneumoniae*. Indeed the mere possession of a policy on antimicrobial restriction policy does not reflect the level of implementation, this being particularly important when co-selection by other agents that are either not restricted or restricted in a different fashion can have a significant selective effect. Support for this hypothesis comes from a study of the correlation between ceftazidime resistant *K. pneumoniae* and the proportion of hospitals possessing an antimicrobial restriction policy together with the implementation of infection control procedures when no correlation was found between these two variables (Larson et al. 2007). The other factor that Rice and colleagues surmised was responsible for undermining the effects of their antimicrobial restriction was the fact that they were dealing with a chronic care facility and there were repeated re-admissions of colonised patients into the ward followed by spread of the organism particularly from faecally colonised patients. The reader is referred to the section above on epidemiology and the importance of infection control preventing cross colonisation

and the difficulty that this poses particularly in chronic care facilities both in terms of implementation and the high rate of faecal carriage of ESBLs by such patients. Restriction of the use of 3GCs and their replacement by drugs like piperacillin-tazobactam have been shown in a number of studies to successfully reduce the occurrence of ESBL-producing bacteria. One of the most significant early studies was that of Patterson and colleagues (Patterson et al. 2000b). This group instituted a very significant reduction in ceftazidime use, when in a 3 months period pre-intervention 4,301 g were used whereas post intervention this reduced to 1,248 g. There was an increase in piperacillin usage from 12,455 to 17,464 g during the same period. This change in usage was reflected in a statistically significant reduction in ceftazidime resistance in *K. pneumoniae* from 42 of 415 isolates (10%) to 19 of 383 isolates (5%) following intervention. Piperacillin resistance also decreased interestingly between the two periods. A similar decrease in ESBL *K. pneumoniae* was observed by Rice and colleagues in a further study (Rice et al. 1996) with a substitution of piperacillin-tazobactam. The group also monitored infection control practices and no changes in infection control practices were observed during that time period. The issue of co-selection is an important one and certainly extremely positive results in controlling ESBL-producing *Klebsiella* ssp. were observed in a large teaching hospital following class restriction of all cephalosporins (Rahal et al. 1998). The restriction of 3GCs and substitution in most therapeutic settings of piperacillin-tazobactam also was reported to result in a marked decrease in the prevalence of ESBL-producing *K. pneumoniae* and *E. coli* in a paediatric hospital in Korea (Lee et al. 2007). Interestingly the effect was more marked for *K. pneumoniae* than for *E. coli*, the suspicion being that the hospital is continuously challenged by community acquired *E. coli* whereas *Klebsiella pneumoniae* is a nosocomial pathogen where the antimicrobial restriction will have a much greater impact. This has certainly been observed in detailed epidemiological studies in Israel (Ben-Ami et al. 2006), where it was observed that much of the ESBL disease seen in the hospital was actually the result of prior colonisation in community health care settings or the wider population.

Blanket controls resulting in large scale reductions in prescribing of cephalosporins and quinolones as well as co-amoxiclav were introduced by the Ministry of Finance in Turkey in 2003. A detailed observational study in a large hospital (Arda et al. 2007) demonstrated a clear reduction in nosocomial infection rates caused by *Klebsiella pneumoniae* whereas resistance to amikacin in *E. coli* and *Acinetobacter baumannii* significantly increased it being assumed as a consequence of the increased use of that drug. A perfect example of the phenomenon sometimes described as “squeezing the balloon”. The practical implementation of antimicrobial restriction is a matter requiring careful consideration, most microbiology and pharmacy departments achieve this by restricted reporting and ward rounds involving pharmacy and medical review of prescribing orders. A computerised antibiotic prescribing programme that blocked repeat prescriptions and those not authorised by id specialists introduced in Korea was claimed to have a significant effect on ESBL-producing *K. pneumoniae* but as in other studies failed to show much impact

on the rates of ESBL *E. coli* (Kim et al. 2008). The type of hospital greatly influences the impact of antimicrobial restriction as in a study of two American hospitals. Antimicrobial restriction had a significant effect on the ESBL rates in the acute medical facility but in the chronic care facility no significant effect was detected despite careful matching of interventions and antimicrobial sub-restriction/substitutions suggesting cross-infection negates the effect of antibiotic stewardship in the elderly care setting (Lipworth et al. 2006). This finding emphasises the importance of infection control measures to control the spread particularly of ESBL-producing *Klebsiella* spp. in a hospital environment.

An alternative approach to restriction or removal of particular classes of antibiotics is to restrict the highly selective antimicrobials such as 3GCs and quinolones but maintain a diversity of prescribing of other classes thus spreading the selective pressure across many different antimicrobial classes and types. In a detailed prospective study in Spain a significant association was found between heterogeneity of antimicrobial prescribing and selection of ESBL-producing *Enterobacteriaceae* (Relative Risk 4.2, CI 1.9–9.3) and *Enterococcus faecalis* (Relative Risk 1.7, CI 1.1–2.9) (Sandiumenge et al. 2006). This supports the important principle in designing antimicrobial restriction policies of ensuring there is a wide range of narrow spectrum agents used wherever possible to dilute the selective pressure of the tendency to overuse of broad spectrum agents for most infections. In a descriptive paper of the long-term experience with ESBL-producing *E. coli and Klebsiella* ssp. in Shrewsbury, England (Warren et al. 2008), the most significant impact on reduction was caused by the opening of a cohort isolation ward rather than antimicrobial restriction which was found to be difficult to enforce at a high level of compliance.

Conclusion

Antimicrobial restriction particularly of 3GCs but also of other cephalosporins and quinolones is an important component in controlling endemic ESBL infection in the hospital environment. It is most important that this intervention is combined with infection control measures such as identification of carriers and application of enhanced hand washing, faeces and urine disposal in those patients, cleaning of the ward environment particularly around those beds occupied by patients with ESBL. Also important is the use of an appropriate active antimicrobial (usually a carbapenem) should patients develop clinically life threatening illness. As ESBL genes particularly $bla_{\text{CTX-M}}$ become embedded in the antibiotic resistance repertoire of *E. coli* either directly associated with peripheral health care systems or "true" community *E. coli* strains then the control of ESBLs becomes much more problematic. This is particularly true if one is to rely purely on antimicrobial restriction as the hospital is being continuously challenged by patients who are colonised who will subsequently develop disease caused by ESBLs (Ben-Ami et al. 2006). The background levels in the community of ESBLs vary widely across the world as do the genotypes

and the host bacterial clones (Hawkey and Jones 2009). Early studies in the UK showed that the diversity of genes present in faecal carriage is much greater than that seen in clinical disease. An early study in York, UK, demonstrated faecal carriage of $bla_{CTX\text{-}M}$-15 14 and 9, although at that point in time clinical infection by $bla_{CTX\text{-}M}$-14 & 9 carrying *Enterobacteriaceae* was rare. This community carriage is an important facet of ESBL control and it can only be potentially reduced by controlling agricultural and community usage of antimicrobials combined with interrupting the natural cycle of *E. coli* through animals and sewage and water and food back into humans. In countries (e.g. India) where there is a very heavy usage of antimicrobials, often without prescription and significant flow of *E. coli* through the ecosphere then the CTX-M ESBL rate is extremely high in both hospital derived isolates (60–70%) and in community isolates (about 30%) (Akram et al. 2007; Ensor et al. 2006). In developing countries with a low usage of selecting antimicrobials such as Malawi a survey of blood culture isolates carried out between April 2000 and March 2005 only found an incidence of ESBL-producing Enterobacteriaceae of 0.7% (Gray et al. 2006). However, localised cross infection and heavy usage of antimicrobials even in this very low incidence background in the developing world, can result in the rapid appearance of much higher rates of carriage of ESBLs, a rate of 28% being reported in a study in an intensive care unit in Tanzania (Ndugulile et al. 2005). Finally, it is clear that throughout the world the incidence of CTX-M producing *Enterobacteriaceae* is increasing, the only exception being some data from voluntary reporting of *E. coli* bacteraemia in the UK which suggests that since 2006 there has been a levelling off in the rate of ESBL-producing *E.coli* at about 10% (http://www.hpa.org.uk/web/HPAWebFile/HPAWeb_C/1274087560639). There has been a major shift in hospital prescribing of antimicrobials in the UK occasioned by the problem of *Clostridium difficile* which has resulted in a marked reduction in prescribing of cephalosporins and quinolones and it could be hypothesised that this has led to a reduction in the occurrence of ESBLs. Interestingly, a study in Dutch patients with uncomplicated UTI in general practice detected a highly significant increase in incidence of ESBL *E. coli* from 0.1 to 1% between 2004 and 2009 despite the Netherlands having a consistently very low usage of antimicrobials (den Heijer et al. 2010). One possible explanation is the marked increase in the occurrence of ESBL *E. coli* in poultry leading to colonisation of individuals in the community (Dierikx et al. 2010). It will be interesting to observe the evolution of these naturally occurring experiments.

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Controlling Hospital-Acquired Infection due to Carbapenem-Resistant Enterobacteriaceae (CRE)

Mitchell J. Schwaber, Yehuda Carmeli and Stephan Harbarth

Abstract CRE impede effective therapy of patients with Gram-negative infections. They affect patients with poor functional status, prolonged hospital stay and multiple exposures to different antibiotic agents. Detecting carbapenemase-mediated carbapenem resistance is a challenge for many microbiology laboratories using automated susceptibility testing systems. To prevent nosocomial and community transmission of CRE, we recommend strict infection control measures—including contact isolation, cohorting of carriers, and dedicated staffing—alongside active surveillance of patients at risk for carriage. Little is known regarding the added value of antibiotic stewardship interventions to control epidemic or endemic transmission of CRE.

Keywords Antibiotic resistance • Acinetobacter • Pseudomonas • KPC • Metallo beta-lactamase • OXA

Background

Carbapenems have the broadest antimicrobial spectrum of any beta-lactam antibiotic and are frequently used as first-line agents for the treatment of severe infections caused by multiresistant Gram-negative bacteria, such as extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. The emergence and spread of carbapenem-resistant Enterobacteriaceae (CRE) are therefore a major concern for patient safety and public health. Infections due to CRE may lead to increased likelihood of treatment failure and growing reliance on third-line agents and combination therapy, with doubtful therapeutic efficacy and increased potential for toxic side-effects (Hartzell et al. 2009). It also increases the cost of treatment, often beyond what can be afforded by patients in low- and middle-income countries. Importantly, at the current moment, CRE differ from most

M. J. Schwaber (✉)
National Center for Infection Control, Israel Ministry of Health, 6 Weizmann Street, 64239 Tel Aviv, Israel
e-mail: mitchells@tasmc.health.gov.il

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_9, © Springer Science+Business Media, LLC 2011

other multidrug-resistant bacterial pathogens in that there is no reliable treatment available (Schwaber and Carmeli 2008). Even more worrisome, the first two cases of panresistant CRE were recently reported from a hospital in New York, illustrating the dilemma of untreatable infections due to these pathogens (Elemam et al. 2009).

In this chapter, we will review important microbiologic and clinical issues related to CRE, and will summarize current evidence on control of these multidrug-resistant Gram-negative pathogens, including issues related to antibiotic stewardship.

Molecular Issues Important for the Understanding of the Spread of CRE

Resistance to carbapenems in Enterobacteriaceae can be caused by a variety of mechanisms, primarily altered outer membrane permeability combined with weakly carbapenem-hydrolyzing beta-lactamases (extended-spectrum or AmpC beta-lactamases), and efficiently carbapenem-hydrolyzing enzymes known as carbapenemases. The most important among these are the serine beta-lactamase KPC, the metallo-beta-lactamases VIM and NDM and the OXA-type beta-lactamase OXA-48. The genes coding for these enzymes are carried by plasmids that often carry other resistance factors as well, resulting in extensively drug-resistant (XDR) bacteria. Since plasmids are readily transferred, these resistance genes can spread within species and even from species to species of Enterobacteriaceae. When such plasmids enter a rapidly disseminating bacterial strain, the result may be a widespread outbreak of an XDR pathogen (Schwaber and Carmeli 2008; Queenan and Bush 2007; http://www.hpa.org.uk/hpr/archives/2009/news2609.htm).

Epidemiology

Non-carbapenemase-producing CRE occurs sporadically, often emerging de-novo under antibiotic selective pressure (Song et al. 2009). These strains, which lack one of the major porins, are believed to be of low epidemic potential. Indeed, only a single outbreak with such a strain has been reported (Lee et al. 2007).

By contrast, although the evolutionary origin of carbapenemases is unclear, their emergence de novo in a specific patient is highly unlikely. Bacteria producing these enzymes can spread readily from patient to patient and have been implicated in numerous outbreaks worldwide, primarily involving *Klebsiella pneumoniae*, but occurring in other species of Enterobacteriaceae as well (Queenan and Bush 2007).

KPC Beta-lactamases

K. pneumoniae producing KPC were first reported in clinical isolates from the eastern United States in the early 2000s (Queenan and Bush 2007), spreading in outbreaks in New York City (Woodford et al. 2004; Bratu et al. 2005). Since then, these pathogens have spread to other US cities, and comprise the main bulk of carbapenem-resistant *K. pneumoniae* isolates, which by 2007 accounted for approximately 10% of all clinical *K. pneumoniae* isolates reported to the National Healthcare Safety Network (Hidron et al. 2008). The majority of outbreaks have been caused by a single MLST type, ST-258, which has also been implicated in outbreaks of more recent onset in other parts of the world (Kitchel et al. 2009; Endimiani et al. 2009; Leavitt et al. 2010). Large outbreaks involving KPC-producing strains of *K. pneumoniae* have since been reported from Israel, Colombia and Greece (Navon-Venezia et al. 2009; Lopez et al. 2011; Giakoupi et al. 2009). Sporadic cases and small outbreaks have been reported from numerous other countries, including China, France, Norway, the United Kingdom, Spain, Italy, Finland, Poland and Germany (Curiao et al. 2010; Wei et al. 2007; Naas et al. 2005; Samuelsen et al. 2009; Woodford et al. 2008; Giani et al. 2009; Osterblad et al. 2009; Baraniak et al. 2009; Wendt et al. 2010). While the majority of KPC-producing Enterobacteriaceae worldwide consists of outbreak strains of *K. pneumoniae*, sporadic cases and small clusters of other KPC-producing Enterobacteriaceae, such as *E. coli* and *Enterobacter* spp., have also been reported (Bratu et al. 2007; Marchaim et al. 2008).

Metallo-beta-lactamases and Oxa-48

VIM-producing *K. pneumoniae* spread rapidly in the early 2000s in hospitals in Greece (Giakkoupi et al. 2003; Ikonomidis et al. 2005), primarily in intensive care units, leading to an increase in carbapenem resistance among bloodstream isolates of over 25% by the middle of the first decade of the century (http://www.rivm.nl/earss/database/). These isolates are usually polyclonal.

The NDM metallo-beta-lactamase has recently been implicated in multiple cases of carbapenem-resistant *K. pneumoniae* found in patients who had been in India (Yong et al. 2009). This finding suggests that CRE due to this mechanism of resistance is spreading in the Indian sub-continent.

Oxa-48-producing *K. pneumoniae* have been the cause of outbreaks in Turkey and have been reported sporadically from other European and Mediterranean countries in recent years as well (Carrer et al. 2008; Cuzon et al. 2008, 2010; Matar et al. 2010).

Even in countries where CRE have become widespread, such as the United States, Israel and Greece, the pathogens are restricted to healthcare settings, without documented spread to the community, even among family members of known carriers. Duration of carriage is variable, and likely depends on patient characteristics such as

underlying illnesses, invasive devices, contact with the healthcare system and antibiotic exposures. In a study carried out in non-acute-care settings, approximately two-thirds of carriers cleared intestinal carriage after 3 months (Ben-David et al. 2011).

Clinical and Public Health Impact

Patients with CRE infection are at high risk of treatment failure and adverse outcomes, including increased mortality and morbidity, longer length of hospital stay, and higher treatment costs when compared to infections caused by susceptible strains. Several studies have reported high percentages of crude in-hospital mortality—some over 50%—among patients infected with CRE (Schwaber et al. 2008; Borer et al. 2009; Patel et al. 2008; Maltezou et al. 2009; Pournaras et al. 2009; Souli et al. 2010; Daikos et al. 2007; Gasink et al. 2009). However, the magnitude of the excess mortality directly attributable to CRE is difficult to quantify as it may be confounded by the severity of the underlying illness, mechanism of resistance, type of carbapenemase, virulence of the infecting clone, adequacy of initial treatment and source control and patient population studied (Daikos et al. 2009; Pitlik 2009). Recently, a study from Cleveland showed that patients with carbapenem-resistant *K. pneumoniae* were elderly, possessed multiple co-morbidities, were frequently admitted from and discharged to post-acute care facilities, and experienced prolonged hospital stays (up to 25 days) with a high mortality rate (up to 35%) (Perez et al. 2010). In particular, microbiologically inappropriate therapy of severe infections caused by CRE may increase the likelihood of death in critically ill patients (Daikos et al. 2009). Table 1 summarizes recent studies that have reported data on important adverse outcomes related to CRE infection.

In addition to the adverse impact of CRE infection on the individual patient, these pathogens have a deleterious effect on public health as well. First, spread of these organisms can limit the ability of hospitals to provide safe care, potentially resulting in closing of intensive care units to new admissions and consequent canceling of elective surgery. Procedures with a high associated risk of infection, including solid organ and hematologic transplantation, may become too risky to justify.

Second, necessary efforts on the part of hospitals to contain the spread of these pathogens will require additional resources, including dedicated personnel in patient cohort areas, isolation rooms, dedicated equipment and additional laboratory investment in microbiologic and molecular identification. Third, the establishment of endemicity of carbapenemase-producing organisms will have an impact on the choice of empiric antibiotics used for all patients with presumed Gram-negative infection, which may necessarily include antibiotics—such as colistin—that are inferior to other agents active against carbapenem-susceptible Gram-negative pathogens.

Fourth, as duration of carriage of these bacteria can be lengthy, spread to long-term care facilities can result in the establishment of continuously augmented reservoirs of carriers who will threaten the safety of non-infected patients in acute

Table 1 Adverse outcomes related to CRE—selected recent articles using a controlled study design

1st author	References #	Setting/population	Cases/controls (n)	Type of infection/pathogens	Impact
Gasink	Gasink et al. (2009)	Tertiary care center in the United States	56/863	All types of nosocomial infection/*K. pneumoniae* (KPC)	KPC-producing *K. pneumoniae* independently associated with in-hospital mortality (AOR, 3.60; 95% CI, 1.87–6.91)
Borer	Borer et al. (2009)	Tertiary care center in Israel	32/32	Bloodstream infection/*K. pneumoniae* (KPC)	Mortality risk ratio of 3.3 (95% CI, 2.9–28.5) associated with bacteremia caused by *K. pneumoniae*
Patel	Patel et al. (2008)	Tertiary care center in the United States	99/99	All types of nosocomial infection/*K. pneumoniae* (KPC)	Case patients more likely than controls to die during hospitalization (48% vs 20%; $P<0.001$) and to die from KPC infection (38% vs 12%; $P<0.001$)
Schwaber	Schwaber et al. (2008)	Tertiary care center in Israel	48/56/59[a]	All types of nosocomial infection/*K. pneumoniae*	After adjustment for severity of illness, CRKP isolation predictive of death (for the CRKP group vs the CSKS group, OR, 3.9; 95% CI, 1.1–13.6; for the CRKP group vs controls, OR, 5.0; 95% CI, 1.7–14.8)
Marchaim	Marchaim et al. (2008)	Tertiary care center in Israel	33/33	All types of infection/*Enterobacter* (KPC)	Imipenem-resistant *Enterobacter* significantly associated with increased mortality in a multivariate model (odds ratio, 8.3 ± 8.6; 95% confidence interval, 1.07–64)
Daikos	Daikos et al. (2009)	3 tertiary care centers in Greece	67/95	Bloodstream infection/*K. pneumoniae* (VIM)	Carbapenem resistance an independent predictor of death (HR, 2.83; 95% CI, 1.08–7.41). After adjustment for inappropriate therapy, resistance non-significant

[a] 48 patients with carbapenem-resistant *K. pneumoniae* (CRKP) isolated; 56 patients with carbapenem-susceptible *Klebsiella* spp. (CSKS) isolated; 59 patients with no *Klebsiella* isolated (controls).

and long-term facilities (Endimiani et al. 2009; Ben-David et al. 2011; Perez et al. 2010). Ultimate spread into the community of pathogens with no effective therapy could transform infections that are currently readily treatable to life-threatening occurrences. Finally, as no new antibiotic class active against Gram-negatives has become available in the past three decades, and no new clear-cut therapeutic options appear on the horizon, the importance of containing the spread of these highly-resistant pathogens is paramount.

Infection Control

The spread of CRE and related microorganisms in the hospital environment represents a serious infection control and therapeutic challenge. Isolation precautions should be implemented and strictly applied to identified carriers, although in several settings simple contact isolation was not sufficient to stop local outbreaks, and cohorting of patients with dedicated staff was warranted (Schwaber 2011; Kochar et al. 2009). Effective tactics to control the spread of CRE include (1) cohorting CRE-colonized and -infected patients, (2) assigning dedicated staff to cohort units, (3) performing active surveillance for CRE by rectal swabs or stool cultures and (4) intensifying hand hygiene and environmental cleaning. In settings in which CRE has established endemicity, infection control efforts should be directed at containing spread outside established areas of isolation using these techniques. In order to be effective in a region with epidemic CRE, infection control guidelines should be uniform for all involved hospitals, and drawn up by a central public health authority invested with the statutory power to oversee and enforce their implementation (Carmeli et al. 2010; Bilavsky and Carmeli 2010).

In settings with low CRE prevalence and localized outbreaks, the aim of infection control measures should be the complete eradication of CRE, according to an adaptation of the classic "search & destroy strategy," whereby patients considered to be at risk of CRE carriage are isolated upon hospital admission pending the outcome of admission screening (Wertheim et al. 2004). Reliable detection of the first CRE index case in a hospital is crucial in order to implement interventions in a timely fashion. Microbiological detection may be challenging (Tenover et al. 2006), thus microbiology laboratories of tertiary care hospitals and reference centers should have a highly sensitive screening method available to reliably detect CRE.

Long-term follow-up should be provided, with re-admission alerts of identified CRE carriers. Continued carriage for re-admitted colonized or infected patients should be assumed unless adequately demonstrated otherwise. Timely dissemination of information at the local, regional and national levels is a cornerstone of effective response. Currently, no strong evidence argues in favor of using either topical or systemic antibiotic decolonization treatment, but further research is needed in this area.

Relationship Between Antibiotic Use and CRE

The causal relationship between antibiotic consumption and increasing incidence of CRE infections is not as straightforward as one may think. It is unclear which classes of antimicrobial agents exert the greatest selection pressure favoring CRE in the gut flora and the hospital environment. A recent study from Pennsylvania demonstrated that prior use of fluoroquinolones (adjusted OR, 3.4) and extended-spectrum cephalosporins (adjusted OR, 2.6) were significant risk factors for infection or colonization with KPC-producing *K. pneumoniae* (Gasink et al. 2009). In another recent study, Falagas et al. compared 53 patients with CRE isolation with 53 matched controls with carbapenem-susceptible *K. pneumoniae* isolation and found that prior exposure to fluoroquinolones and antipseudomonal penicillins were independent risk factors for CRE infection (Falagas et al. 2007). In a recent outbreak report from Greece, a beta-lactam/beta-lactamase inhibitor combination was the most frequently administered antimicrobial prior to isolation of KPC-producing *K. pneumoniae* (20 patients; 42.5%), whereas only nine patients (19.1%) had prior carbapenem use (Pournaras et al. 2009).

Other studies found divergent results. For instance, several reports associated prior carbapenem use with isolation of CRE (Schwaber et al. 2008; Patel et al. 2008). In an outbreak of metallo-beta-lactamase-producing bacteria reported from Australia, 75% of the colonized or infected patients had received carbapenems before isolation of the resistant bacterium (Peleg et al. 2005). In an earlier study of the risk factors for CRE isolation, Kwak et al. evaluated 30 patients with nosocomial CRE isolation in South Korea and found that previous exposure to carbapenem and cephalosporin antibiotics was associated with CRE acquisition, while fluoroquinolone exposure was protective (Kwak et al. 2005). Like Falagas et al. (2007) and unlike Kwak et al. (2005), Schwaber et al. found that exposure to a fluoroquinolone was independently predictive of CRE isolation (Schwaber et al. 2008).

Overall, uncertainties persist in individual patient-level analyses regarding which prior antibiotic exposures are most important as risk factors for acquisition of, transmission of and infection with CRE. Similarly, ecologic studies using aggregate data-level analyses do not show a clear-cut picture. For instance, US healthcare institutions are not very big consumers of carbapenems, yet they have very high CRE rates (Hidron et al. 2008; Pakyz et al. 2008). By contrast, German ICUs use carbapenems widely and yet still have a very low prevalence of CRE (Meyer et al. 2010).

Antibiotic Stewardship

Notwithstanding the methodological differences and divergent findings of various studies, several reports have now suggested a correlation between prior antibiotic use and CRE colonization and resistance. Thus, the question arises whether active antibiotic restriction or other antimicrobial stewardship interventions can help to

control the spread of CRE within different healthcare settings. Surprisingly, at the current moment, there is a paucity of data available to answer this question. Only a few studies have dealt with this issue, without providing any strong evidence. No study with a controlled design has been conducted so far to establish the role of antibiotic stewardship in CRE control. The paucity of published reports on this topic stands in contrast to the abundant literature on ESBL control attempted via changing antibiotic formularies or implementing antibiotic restriction and rotation (Davey et al. 2006).

A study from New York City reported successful control of KPC spread using diverse infection control interventions without antibiotic restriction. The authors underlined that antimicrobial usage remained the same throughout the study period, suggesting that changes in antimicrobial pressure did not account for the decrease (Kochar et al. 2009). Similarly, Munoz-Price et al. reported successful control of an outbreak of KPC-producing *K. pneumoniae* at a long-term acute care hospital without antibiotic stewardship interventions (Munoz-Price et al. 2010).

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Control of Multi-Drug Resistant *Acinetobacter* Infections

Paschalis Vergidis and Matthew E. Falagas

Abstract Although initially considered to be of low virulence, *Acinetobacter* is being increasingly implicated in severe infections, particularly among hospitalized patients. Infection with *Acinetobacter baumannii* is associated with increased mortality. Multi-drug resistant strains have emerged worldwide and prior antibiotic use has been identified as a significant risk factor for resistance. Carbapenems are the mainstay of treatment for severe infections. However, carbapenem-resistant strains are emerging. Tigecycline may not be consistently active against those resistant isolates. A considerable proportion of multi-drug resistant *A. baumannii* strains are only susceptible to polymyxins. Combination treatment has been used, but there is no clear evidence of its superiority over monotherapy. Antimicrobial stewardship programs are necessary to prevent emergence of resistance. Certain factors, such as patient population characteristics specific to a hospital, may play an important role in the effectiveness of antimicrobial stewardship. An important strategy to minimize redundant exposure to antimicrobials is to de-escalate from broader to more targeted therapy, once susceptibility testing results are available. Besides antimicrobial stewardship, any attempt to control the spread of resistant *Acinetobacter* should include intensive infection control measures.

Keywords *Acinetobacter* • Antibiotic resistance • Hospital acquired infections • Antibiotic stewardship • Colistin • Tigecycline

Introduction

The genus *Acinetobacter* comprises strictly aerobic, Gram-negative, non-motile, non-lactose-fermenting, oxidase-negative, catalase-positive coccobacilli. More than 30 genomic species have been identified. *Acinetobacter baumannii* is the species mainly associated with human disease. *A. baumannii* is ubiquitously found in the environment, can survive on inanimate surfaces, and may infrequently colonize the skin of healthy individuals. Although initially considered to be of low virulence,

M. E. Falagas (✉)
Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 15123 Marousi, Athens, Greece
e-mail: m.falagas@aibs.gr, falagas@tufts.edu

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_10,

these organisms have been increasingly implicated as pathogens. Infections are typically encountered in hospitalized patients, especially those critically ill, but can also occur in the community, mainly in tropical climates. Risk factors for infection include advanced age, immunosuppression, prolonged hospital stay, major trauma or burn injuries, mechanical ventilation, performance of invasive procedures, presence of indwelling catheters, and prior antimicrobial use. Common routes of transmission include contaminated medical devices such as indwelling catheters, ventilators, and ventilation devices.

Clinical Manifestations

The main clinical syndromes include pneumonia and bloodstream infection. *Acinetobacter* has been the causative agent of healthcare-associated pneumonia, particularly in patients on mechanical ventilation for a prolonged period of time (Garnacho-Montero et al. 2005). These patients are usually colonized before development of infection. Pneumonias tend to be multilobar. Nosocomial bloodstream infections due to *Acinetobacter* are most commonly associated with pneumonia or a catheter-related infection. A source cannot be indentified in almost 50% of the cases (Wisplinghoff et al. 2000). Bacteraemias typically occur in critically ill patients and can be associated with septic shock. *Acinetobacter* spp. are a rare cause of endocarditis.

Acinetobacter is being increasingly recognized as the cause of post-operative or traumatic wound infections. These may be associated with presence of foreign material. Extension to deeper tissues may lead to osteomyelitis. Colonization of the urinary tract is common in hospitalized patients with indwelling urinary catheters. Nonetheless, cystitis or pyelonephritis are uncommon. Finally, *Acinetobacter* can cause meningitis, usually after head trauma or neurosurgical procedures, especially in the presence of ventricular draining tubes. *Acinetobacter* peritonitis can occur in the presence of peritoneal dialysis catheters. Other manifestations include septic arthritis, sinusitis (typically in patients on prolonged endotracheal intubation), keratitis (which can be associated with corneal ulceration or use of contaminated contact lenses), and endophthalmitis.

Epidemiology and Mechanisms of Resistance

Data from the US National Nosocomial Infections Surveillance system showed a consistently increasing proportion of *Acinetobacter* infections among all other Gram-negative organisms and across all hospitals. Specifically, the cases of pneumonia in the intensive care unit (ICU) increased significantly from 4% in 1986 to 7% in 2003 (Gaynes and Edwards 2005). Increasing resistance of *Acinetobacter* to antimicrobial agents has been widely noted. Further complicating the issue,

Acinetobacter infections have been associated with outbreaks in the healthcare setting, mainly in the ICU setting (Fournier and Richet 2006). Specific resistant clones are a common cause of outbreaks.

The term multi-drug resistant *A. baumannii* lacks a consensus definition, but is generally characterized as the presence of resistance to at least three classes of antimicrobials that would otherwise serve as treatment for *Acinetobacter* infections (Falagas et al. 2006a). The term pandrug-resistant *Acinetobacter* has been used to describe *Acinetobacter* strains that are resistant to all standard antimicrobial agents, including polymyxins. Resistance mechanisms include β-lactamases, alterations in outer membrane proteins (porins), and efflux pumps (Bonomo and Szabo 2006). Clinically most troubling are acquired β-lactamases, including serine and metallo-β-lactamases, which confer resistance to carbapenems. Unlike other Gram-negative pathogens, inducible AmpC expression does not occur in *A. baumannii* and AmpC β-lactamases are not associated with clinically significant resistance. Resistance to aminoglycosides is caused by aminoglycoside-modifying enzymes which impair drug binding to its target site. Tigecycline is the substrate of an emerging multi-drug efflux system (Peleg et al. 2007). Finally, resistance to quinolones occurs through mutations in the genes *gyrA* and *parC* that result in modifications of the DNA gyrase and topoisomerase IV, respectively.

Antimicrobial resistance is more extensive in isolates from ICU patients in Asia and Latin America and certain European countries (Jones et al. 2004; Tognim et al. 2004; Wang and Chen 2005). In a surveillance report from 48 European hospitals for the period 2002–2004, 73.1% of isolates were susceptible to meropenem, 69.8% were susceptible to imipenem and only 32.4% to ceftazidime (Unal and Garcia-Rodriguez 2005). Less extensive antimicrobial resistance has been reported for isolates from ICU patients in the USA, the Netherlands and the Nordic countries (Friedland et al. 2003). In the US, infections due to *Acinetobacter* have been documented in returning military personnel who were deployed to Iraq or Afghanistan. Indeed, isolates cultured from inanimate surfaces in field hospitals have been genotypically linked to patient isolates (Scott et al. 2007).

Antibiotic Overuse as a Risk Factor for Emergence of Resistance

In a systematic review of the literature, prior antibiotic use was identified as a significant risk factor for acquisition of multi-drug resistance (Falagas and Kopterides 2006). In 20 case-control studies multivariable analysis was performed. In 11 of those studies, prior antibiotic use was the most common risk factor for multi-drug resistance. Third-generation cephalosporins and carbapenems were most commonly associated with emergence of resistance. The odds ratio of carbapenem use being a risk factor was found in the range of 4–10. Other risk factors included ICU stay, mechanical ventilation, and severity of illness. In eight studies, univariate analysis was performed and again prior antibiotic use was identified as an important

risk factor. In 27 studies of *A. baumannii* outbreaks, environmental contamination was identified as the predominant factor. Prior use of antibiotics was found to be important in five of these studies.

The lessons learned regarding antibiotic stewardship in a 1,000-bed hospital in Barcelona, Spain, may be applicable to other settings. A sustained outbreak of resistant *Acinetobacter* infections led to increased use of carbapenems to which the isolates were initially susceptible. The outbreak begun in 1992 and by 1997 carbapenem-resistant *Acinetobacter* had emerged and disseminated (Corbella et al. 2000). Molecular typing actually revealed the introduction of two new epidemic clones. Prior carriage of carbapenem-resistant organisms and treatment with carbapenems were found to be the most significant risk factors in multivariate analysis. A multicomponent infection control program, that included restriction of carbapenem use, was instituted. This led to an 85% decrease in mean monthly carbapenem use and subsequently to a substantial decrease in the incidence of infection or colonization with *Acinetobacter*.

The emergence of multi-drug resistant strains has led to the re-use of colistin, frequently as the last resort for treatment of these isolates. In a matched case-control study from our group, colistin use was independently and strongly associated with the isolation of colistin-resistant *A. baumannii* (Matthaiou et al. 2008). Studies on the appropriate dosing and duration of treatment with colistin as well as its role in combination therapy should be undertaken.

Mortality

The current evidence suggests that infection with *A. baumannii* in hospitalized patients is associated with increased attributable mortality (Falagas et al. 2006b; Falagas and Rafailidis 2007). Compared to *Klebsiella pneumoniae* bacteraemia, *A. baumannii* bacteraemia was associated with higher all-cause 30-day mortality (Robenshtok et al. 2006). Subgroup analyses confirmed the association of *A. baumannii* with increased mortality even in less severely ill patients, namely those not presenting with septic shock and those not mechanically ventilated. In another study, increased mortality among patients receiving inappropriate empiric treatment for *A. baumannii* bacteraemia was noted (Falagas et al. 2006c). No statistically significant difference was reported in this study probably due to the small number of patients.

A retrospective, risk-adjusted, cohort study of 80 patients with *Acinetobacter* bacteraemia conducted in Korea demonstrated that those infected with imipenem-resistant strains had a significantly higher 30-day cumulative mortality rate than those infected with imipenem-susceptible strains (57.5% versus 27.5%) (Kwon et al. 2007). This was mainly due to a higher rate of inappropriate antimicrobial therapy. Most isolates resistant to imipenem were multi-drug resistant. Indeed, in facilities with a high prevalence of multi-drug resistant *A. baumannii* isolates, the

use of more aggressive empirical antimicrobial treatment may be justified from the outset, particularly in the ICU setting.

Antimicrobial Treatment

Common treatment options for *Acinetobacter* infections include carbapenems, sulbactam, antipseudomonal penicillins, antipseudomonal cephalosporins, aminoglycosides, quinolones, polymyxins, tetracyclines, and tigecycline (Michalopoulos and Falagas 2010). Antimicrobial treatment should be tailored based on susceptibility testing results. Carbapenems are the mainstay of treatment for severe infections. However, carbapenem-resistant *A. baumannii* strains have emerged worldwide (Gales et al. 2001; Van Looveren and Goossens 2004). Sulbactam is a β-lactamase inhibitor with intrinsic bactericidal *in vitro* activity against *Acinetobacter*. Nonetheless, the activity of sulbactam has declined substantially, especially in carbapenem-resistant isolates. Aminoglycosides have shown moderate rates of antimicrobial activity and have mainly been used in cases of bacteraemia or meningitis in combination with other antimicrobials.

A considerable proportion of multi-drug resistant *A. baumannii* strains are susceptible only to polymyxins, which prompted the use of an old antibiotic in recent years. The major adverse events of colistin are nephrotoxicity and neurotoxicity. Recent clinical studies have found less colistin-associated toxicity than originally reported (Falagas and Kasiakou 2006). High rates of susceptibility of *A. baumannii* to tigecycline, a new glycylcycline antibiotic, have been demonstrated in large surveillance trials (Farrell et al. 2008). However, tigecycline may not be consistently active against imipenem-resistant *Acinetobacter* isolates. As recent clinical trials have indicated poor clinical or microbiological outcomes, further studies on its use are needed.

The combination of imipenem with sulbactam (Song et al. 2007), colistin with a carbapenem (Yoon et al. 2004), or colistin with minocycline (Tan et al. 2007) have shown synergistic effect *in vitro*. Similarly the combination of imipenem with tobramycin in a pneumonia murine model (Montero et al. 2004), and the combination of meropenem and sulbactam in a murine model of intraperitoneal infection (Ko et al. 2004) have been shown to be effective. Combination treatment has been used in clinical practice, but there is no clear evidence of its superiority over monotherapy.

Antimicrobial Stewardship

Several lines of evidence demonstrate a causal relationship between antimicrobial use and emergence of resistance. The increasing prevalence of multi-drug resistant pathogens in combination with the lack of new drugs for Gram-negative organ-

isms, led to the introduction of antimicrobial stewardship programs. There are two core strategies: (1) prospective audit with intervention and feedback, (2) formulary restriction and preauthorization (Dellit et al. 2007). These strategies are not mutually exclusive. Antimicrobial stewardship may involve different interventions, commonly combined with rigorous infection control measures. Hence it may be difficult to discern the contribution of each intervention in controlling the spread of antimicrobial resistant pathogens. In a systematic review of antimicrobial prescribing (Davey et al. 2006), a decrease in *Clostridium difficile*-associated diarrhea was most consistently shown. The study suggested that antimicrobials play a major role in selection of Enterobacteriaceae expressing extended-spectrum β-lactamases (ESBL), an intermediate role in vancomycin-resistant Enterococci, and a minimal role in methicillin-resistant *Staphylococcus aureus*. Nonetheless, further research is needed in this area.

Prospective audit with intervention and feedback to the prescriber has been shown to be effective in both large teaching hospitals (Solomon et al. 2001) and medium-sized community hospitals (Carling et al. 2003). In smaller hospitals, a program that involves periodic auditing of patients receiving multiple antimicrobials for a prolonged period is feasible. Finally, computer surveillance, where available, may aid in identification of patients receiving specific drugs or combinations thereof and facilitate antimicrobial stewardship. These interventions give the opportunity of practitioner education and may improve prescribing practices in the long term. Restrictive policies include formulary restriction and preauthorization requirements for specific antimicrobial agents. These policies have been shown to be effective in reducing cost (Coleman et al. 1991). However, the effect on decreasing antimicrobial resistance has not been as clear. Restriction may actually cause a shift to the use of alternative agents and result in resistance to these antimicrobials.

Certain factors, such as patient population characteristics specific to a hospital, may play an important role in the effectiveness of antimicrobial stewardship. Investigators observed a significant difference in the decrease of ESBL-producing organisms in two hospitals in Philadelphia, Pennsylvania, after restriction of ceftriaxone and ceftazidime use (Lipworth et al. 2006). This was attributed to the larger number of patients from long-term care facilities who were admitted to the hospital with the lower success rates. Increased incidence of patients with cultures positive for cefotaxime-resistant *Acinetobacter* spp. was unexpectedly found after implementation of a program that resulted in decreased usage of cephalosporins and imipenem, and increased usage of beta-lactam/beta-lactamase-inhibitor combinations (Landman et al. 1999). Hence, close surveillance for emergence of new resistant pathogens should be continued even after changes in antimicrobial use policies.

Among the supplemental strategies, there are insufficient data to support the routine use of antimicrobial cycling or combination treatment in order to reduce emergence of resistance. On the other hand, dose optimization based on pharmacokinetic/pharmacodynamic parameters as well as individual patient characteristics is recommended. For example, in the case of colistin, dosing recommendations are based on data acquired more than three decades ago, without taking into consideration current pharmacodynamic principles. Colistin exerts its antimicrobial ef-

fect in a concentration-dependent manner; hence subinhibitory concentrations of colistin may promote the emergence of resistance, particularly in sites of infection where drug penetration might be compromised. Another consideration is that dose optimization may target a specific pathogen which is thought to be involved in a certain infection. Other co-infecting pathogens or colonizing microorganisms may not be targeted by the specific drug program and thus be amenable to emergence of resistance.

De-escalation from broader to more targeted therapy, once susceptibility testing results are available, is another strategy to minimize redundant exposure to antimicrobials. De-escalation may involve discontinuation of antimicrobial treatment if culture results are negative and no other compelling evidence of infection. It should be noted that *Acinetobacter* may colonize the skin, pharynx or gastrointestinal tract. The organism may also colonize medical devices such as tracheostomy or endotracheal tubes. The possibility of colonization should be taken into account when interpreting culture results. Potential environmental contamination should also be considered. Isolation of *Acinetobacter* from colonized patients does not necessitate treatment. This applies particularly to chronically ventilated patients.

Infection Control Measures

Besides antimicrobial stewardship, any attempt to control the spread of resistant *Acinetobacter* should include intensive infection control measures. Hand hygiene is of paramount importance. Compliance of health care workers can be improved with the use of handrub antiseptic solutions placed at the bedside or outside the patient's room. Implementation of contact isolations of infected or colonized patients can also aid in controlling the infection. Regarding environmental cleaning, *Acinetobacter* is largely susceptible to disinfectants; however these should be used at appropriate concentrations and adequate exposure to the agent should be allowed. Disinfection of medical equipment, especially mechanical ventilators, should be meticulous. In case of an outbreak, if a primary source can be identified, it should be eliminated. Even then, infection control measures need to be implemented for a long period of time and may require closure of hospital units. Finally, the epidemic strain should be treated with appropriate antimicrobials. The use of aggressive infection control makes it difficult to assess the relative efficacy of each individual measure. Nonetheless, a comprehensive strategy is usually required due to the complexity of the outbreaks.

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The Control of Multidrug-Resistant *Pseudomonas*: Insights into Epidemiology and Management

Evangelos J. Giamarellos-Bourboulis

Abstract Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has emerged as a nosocomial pathogen. It is the third most common cause of invasive infections in the Intensive Care Unit (ICU) and the second most common cause of health-care associated pneumonia. Epidemiological studies reveal that the acquisition of these isolates may be either endogenous in 55% of cases or exogenous in 45% of cases. Endogenous acquisition results from the effect of prior administration of antimicrobials on bacterial flora, namely fluoroquinolones and carbapenems. Exogenous acquisition results after cross-transmission from a common environmental source. Available therapeutic options for the management of infections by MDR *P. aeruginosa* are limited to the administration of polymyxins. Limitation of spread of these isolates relies on the combination of several strategies consisting of rotation of empirically prescribed antimicrobials, early recognition and containment of outbreaks and isolation of contaminated patients.

Keywords HAI • VAP • HAP • UTI • Antibiotic stewardship • Immunomodulation

Introduction and Terminology

Infections by multidrug-resistant (MDR) *Pseudomonas aeruginosa* are widely emerging as a serious problem in the health-care setting. This species was originally described as a cause either of nosocomial infections or of infections in the immunocompromised host. This epidemiology has been broadened nowadays to comprise not only infections taking place during hospitalization but also infections occurring among patients living in any health-care setting. These health-care associated infections are caused by members of the bacterial flora of these patients that resemble common nosocomial flora. That flora changes when patients stay in long-term care facilities (LTCF), they undergo continuous ambulatory peritoneal dialysis or hemofiltration, and they even receive parenteral antimicrobials

E. J. Giamarellos-Bourboulis (✉)
4th Department of Internal Medicine, ATTIKON University Hospital, 1 Rimini Street, 124 62 Athens, Greece
e-mail: egiamarel@med.uoa.gr

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_11, © Springer Science+Business Media, LLC 2011

treatment at home. A recent survey in 41 LTCFs in Athens, enrolling 1,523 residents disclosed carriage of MDR *P. aeruginosa* in the decubitus ulcers of 1.5% (Kanellakopoulou et al. 2009).

The level of resistance of *P. aeruginosa* to more than two classes or antimicrobials is defined as either multidrug-resistance (MDR) or extensive drug-resistance (XDR) or pandrug-resistance (PDR). There is no consensus as to what each of these levels precisely signify for *P. aeruginosa* species since the only species for which a consensus exist for that definition is *Mycobacterium tuberculosis*. The definitions applied in this chapter are those widely accepted by most authors. According to them, an isolate of *P. aeruginosa* is MDR when it is resistant to three or more chemically distinct classes of antimicrobials. These antimicrobials classes are antipseudomonal penicillins, 3rd and 4th-generation cephalosporins, fluoroquinolones mainly ciprofloxacin and aminoglycosides. XDR isolates are resistant to all but one class of antimicrobials with antipseudomonal activity. PDR isolates are resistant to all clinically available antimicrobial agents.

Nosocomial *P. aeruginosa* may be either multidrug-resistant (MDR) or pandrug-resistant (PDR). MDR isolates are generally resistant to three or more chemically distinct classes of antimicrobials but they are susceptible to polymyxins. These antimicrobial classes are antipseudomonal pencillins, 3rd and 4th generation cephalosporins, carbapenems, fluoroquinolones (mainly ciprofloxacin) and aminoglycosides. PDR isolates are resistant to all antimicrobials with endogenous antipseudomonal activity. The present chapter aims to provide all recent data in the literature about these MDR and PDR variants of this species related to their epidemiology, pathogenesis of infection and management.

Epidemiology of Infections by MDR *Pseudomonas aeruginosa*

Extent of the Problem

The incidence of invasive infections by MDR *P. aeruginosa* differs considerably from one country to another. In the European Union, this percentage ranges between 10 and 25% for countries like Germany, France, Spain and Italy; it rises up to 50% in Poland and surpasses 50% in Greece and Turkey (Gould 2008). In the latter three European countries most of these isolates are also XDR. *P. aeruginosa* is the third more common cause of invasive infections in the Intensive Care Units in Canada representing 10% of isolates; 12.6% of these isolates are MDR (Zhanel et al. 2008). In Spain, 18.9% of all *P. aeruginosa* isolates collected as part of a nationwide surveillance of resistance were resistant to carbapanems. Most of these isolates were derived form patients with hospital-acquired infections mainly in the Intensive Care Unit (ICU) (Gutiérrez et al. 2007). A national surveillance study in ICUs in USA disclosed a 21% prevalence of MDR *P. aeruginosa* in 2002 (Lister et al. 2009).

P. aeruginosa is the second most common cause of health-care associated pneumonia, of hospital-acquired pneumonia and of ventilator-associated pneumonia (VAP). It is also reported as the cause of 9% of hospital-acquired urinary tract infections (UTIs). That species also affects populations with special predisposition like those suffering from hematologic malignancies, cystic fibrosis and bronchiectasis (Driscoll et al. 2007).

It should be underscored that the emergence of PDR isolates of *P. aeruginosa* in Europe is extremely limited (Souli et al. 2008).

Modes of Transmission and Predisposing Factors

Despite the existing controversies in the literature about the mechanism of spread of MDR *P. aeruginosa*, definite answers derive only after molecular typing of the isolates. Mechanism of resistance should also be defined including the production of metallo-β-lactamases (MBL), the detection of class 1 integrons, the production of AAC (6′) enzymes acetylising the aminoglycoside molecules and the detection of *gyr*A and *par*C genes conferring resistance to fluoroquinolones.

After an extensive literature search in MedLine, eight outbreaks of MDR *P. aeruginosa* have been described from 2005 to 2009. These outbreaks occurred either in patients hospitalized in the general ward or in patients hospitalized in an ICU. The characteristics of these outbreaks and predisposing factors for the acquisition of MDR isolates are shown in Table 1. In the same Table predisposing factors for cross-transmission are described.

It is estimated that the rate of colonization and/or infection by MDR *P. aeruginosa* is 0.5 episodes/1,000 patient-days in the general ward and 29.9 to 36.7/100 patients in the ICU (Agodi et al. 2007; Peña et al. 2009). The majority of these isolates are of the O11 serotype. This surveillance data along with the outbreak characteristics are described in Table 1, endogenous colonization occurring in almost 55% of cases in the ICU and exogenous transmission occurring in almost 45% of cases in the ICU. The main factor predisposing to endogenous colonization is prior antibiotic consumption leading to destruction of bacterial intestinal flora (Donskey 2006). The whole process is facilitated as the duration of hospitalization increases so that the odds ratio (OR) for colonization by MDR *P.aeruginisa* is 1.50 per week of stay in the ICU (Parker et al. 2008). Implicated antibiotics for the acquisition of XDR *P. aeruginosa* when a patient is hospitalized in the general ward are fluoroquinolones. These antibiotics are fluoroquinolones, carbapenems and colistin regarding patients staying in an ICU (Gasink et al. 2007). In a survey of 346 patients hospitalized for more than 48 h in two medical ICUs, surveillance cultures were taken from nares, pharynx, rectum and from tracheobronchial secretions to estimate the colonization rate by MDR *P. aeruginosa*. It was estimated that the main factors significantly associated with colonization were enteral nutrition (OR: 11.4), use of piperacillin/tazobactam for 3 days or longer (OR: 2.6) and administration of amikacin for 3 days or longer (OR: 2.6) (Martínez et al. 2009).

Table 1 Characteristics of outbreaks by multidrug-resistant *Pseudomonas aeruginosa* among patients residing in the general ward and among patients hospitalized in an Intensive Care Unit

	Number of patients	Resistance profile	Number of genotypes	Predisposing factors	Cross-transmission
General ward					
Peña et al. 2009	246[a]	66% MDR	ND	Prior hospitalization (OR: 2.7) Prior use of fluoroquinolones (OR: 2.6)	ND
Sekiguchi et al. 2007a	284	75.4% MDR	3	ND	ND
Sekiguchi et al. 2007b	23	100% MDR	13	ND	Handling of biological fluids
Intensive Care Units					
Agodi et al. 2007	138	72.55% XDR	18	Prior use of carbapenems (OR: 3.4)	44.1% of cases
Bou et al. 2006	17	76.4% MDR	5	Prior use of antimicrobials	Contaminated Bronchoscope
Metzelopoulos et al. 2007	5	100% PDR	1	Prior use of colistin (OR: 76) Prior use of carbapenems (OR: 12.0)	Open suctioning procedures
Shimono et al. 2007	7	100% MDR	1	ND	Contaminated Bronchoscope

ND not defined, *MDR* multidrug-resistant, *XDR* extensive drug-resistant, *PDR* pandrug-resistant, *OR* odds ratio

[a] Outbreak was reported in 19 hospitals

Exogenous cross-transmission from one patient to another takes place by the hands of the nursing personnel, contaminated by open drainage and suction or by handling biological fluids like urine.

Main Resistance Mechanisms

P. aeruginosa is endogenously susceptible to a limited number of antimicrobials. MDR isolates possess two or more different mechanisms of resistance. A synopsis of these mechanisms is given below (Lister et al. 2009):

- Over-production of AmpC β-lactamase hydrolyzing all β-lactams with the exception of carbapenems
- Loss of OprD conferring resistance to imipenem. OprD is an outer membrane porin of the bacterial cell. Its loss confers resistance to imipenem. Other carbapenems, like meropenem and doripenem, may enter the bacterial cell through another porin so that loss of OprD is not always linked to resistance to meropenem and to doripenem.
- Production of acetyltransferases and adenyltransferases which inactivate aminoglycosides.
- Mutations of the gyrase A and topoisomerase IV encoded by genes *gyrA* and *parC* respectively conferring resistance to fluoroquinolones. Cross-transmission of quinolone resistance by other species with plasmids has not been reported (Poirel et al. 2008)
- Efflux pumps conferring resistance to a variety of antimicrobials. Efflux pumps belong to the RND (resistance-nodulation-division) superfamily consisting of three or more proteins working together and aiming to pump antimicrobial molecules outside the bacterial cell. Ten efflux pumps have been described. The best studied are MexAB-OprM, MexCD-OprJ, MexEF-OprN and MexXY. The first confers resistance to fluoroquinolones, β-lactams, β-lactamase inhibitors, tetracyclines, chloramphenicol, macrolides and trimethoprim; the second confers resistance to fluoroquinolones, β-lactams, tetracycline, chloramphenicol, macrolides and trimethoprim; the third confers resistance to fluoroquinolones, chloramphenicol and trimethoprim; and the fourth confers resistance to fluoroquinolones, β-lactams, tetracycline, aminoglycosides, macrolides and chloramphenicol.

Clinical Significance of MDR *P. aeruginosa*

A variety of clinical studies both prospective and retrospective in design end up with the conclusion that infections by MDR *P. aeruginosa* have a significant impact on mortality. A retrospective study of our group in non-neutropenic hosts in

the general ward disclosed 22.2% mortality of infections by MDR *P. aeruginosa* compared to 0% of infections by susceptible isolates (Giamarellos-Bourboulis et al. 2006). For ICU infections caused by MDR *P. aeruginosa* mortality ranges between 22% and 77%; this ranges between 12% and 23% when ICU infections are caused by susceptible isolates (Shorr 2009).

A debatable question is whether increased mortality of infections by MDR isolates is due to either an effect of the resistance mechanisms on the virulence of the species or the lack of available antimicrobial agents. In a cohort of 37 ICU patients with various types of infection, it was found that both colonization and infection by XDR *P. aeruginosa* was a major driver to death (Wang et al. 2006). Two more studies have been published on the impact of resistance in mortality. The first study was a cohort of 108 patients with bacteremia caused by isolates resistant to imipenem. Analysis revealed that the advent of severe sepsis was a major driver for death more significant than the administration of appropriate antimicrobial chemotherapy (Suárez et al. 2009). The second study comprised 120 patients with bacteremia. Results showed that the offending isolates remained fully pathogenic despite the existence of more than two diverse resistance mechanisms (Hocquet et al. 2007).

In vitro studies of our group have shown that innate immune responses differ after challenge by susceptible and MDR *P. aeruginosa*. More precisely, eight susceptible and 12 MDR isolates were selected, all with different PFGE patterns of their DNA. Monocytes of healthy donors were stimulated in vitro by these isolates. Release of pro-inflammatory mediators mainly interleukin (IL)-1β and IL-6 was greater after stimulation by susceptible than by MDR isolates. Several of these isolates were used for challenge in a model of intraperitoneal sepsis in mice and bacteremia in rabbits. Survival of animals was prolonged after infection by MDR than by susceptible isolates (Giamarellos-Bourboulis et al. 2004a, b).

Part of the pathogenesis of infections by MDR *P. aeruginosa* is mediated through the production of alginate, allowing adherence to external surfaces like urinary catheters, tubes of mechanical ventilation and central vascular catheters. Alginate is produced when isolates produce some molecules working like inter-bacterial signals. The best studied molecules are homoserine lactones known as quorum sensors. Alginate produced by each isolate creates a biofilm surrounding bacteria and allowing strict adherence to external surfaces. By the same biofilm lower airways of patients with cystic fibrosis and bronchiectasis are colonized by *P. aeruginosa* (Driscoll et al. 2007).

Management of MDR *P. aeruginosa*

Therapeutic Options

It is evident that the selection of antimicrobials for the management of infections by MDR *P. aeruginosa* is limited. There is no doubt that the most difficult-to-treat

infection caused by MDR isolates is nosocomial pneumonia, mainly VAP. Empirical treatment of VAP relies on the administration either of monotherapy or of combination therapy. A recent randomized trial failed to define a difference between the monotherapy versus combination treatment for the outcome of VAP. However, secondary analysis revealed patients' benefit from combination treatment when VAP was caused by MDR microorganisms. Benefits consisted of greater clinical resolution and shorter ICU stay although overall mortality was not affected (Heyland et al. 2008).

As a consequence, the need for the empirical prescription of combination therapy should be confined to patients with a high likelihood to be infected by MDR isolates. A prediction tool has been proposed for the likelihood that nosocomial pneumonia is caused by MDR *P. aeruginosa*. This tool has been developed based on the epidemiology and predisposing factors for acquisition of MDR species. The tool takes into account two main factors: length of hospital stay (LOS) and the number of antibiotic exposures. Significant antibiotic exposures were previous carbapenem for ≥3 days; of fluoroquinolone for ≥4 days; aminoglycoside for ≥5 days; cefepime for ≥9 days; and piperacillin/tazobactam for ≥12 days. As a consequence it is proposed that the expected likelihood for patients to develop MDR *P. aeruginosa* VAP with LOS<33 days and one antibiotic exposure is 25.2%; and for patients with LOS<33 days and two antibiotic exposures is 33.4%. For patients with LOS≥33 days and nil antibiotic exposures the expected likelihood is 35.4%; for patients with LOS≥33 days and one antibiotic exposure is 47.0%; for patients with LOS≥33 days and two antibiotic exposures is 62.3%; and for patients with LOS≥33 days and three antibiotic exposures is 82.7% (Lodise et al. 2007).

Polymyxins

Polymyxins are polypeptide antibiotics that act as detergents on the bacterial cell wall. They were introduced in 1940 but they were abandoned in the 1980s due to the occurrence of nephrotoxicity and neurotoxicity. They retain excellent in vitro activity against MDR *P. aeruginosa* and they have been proposed as the only salvage therapy for infections by XDR species (Walkty et al. 2009). Five peptides are available, namely A to E, of which polymyxin B and colistin (polymyxin E) are clinically used. The most widely used preparation is colistimethate and colistin methanesulfonate (CMS). One million units of CMS correspond to 80 mg and the recommended intravenous regimen is 240 mg every 8 h. This dose should be adjusted for patients with renal failure. Colistin may also be administered in a nebulized form.

A major problem for the evaluation of the clinical efficacy of colistin for the management of infections by MDR *P. aeruginosa* is the lack of prospective randomized clinical trials. Reported clinical efficacy is based on retrospective analysis of series of patients (Landman et al. 2008). According to them, clinical success with colistin ranges between 58 and 80%, being higher for patients with acute pyelo-

nephritis and lower for patients with nosocomial pneumonia (Levin and Oliveira 2008). The clinical efficacy of colistin depends on favorable pharmacokinetic/pharmacodynamic relationship for which data are lacking. A recent pharmacokinetic study of the 240 mg tid regimen of CMS in critically ill patients without renal failure showed that for the first 8 h serum drug levels remained at sub-therapeutic levels. Only after 8 h, when steady state supervened, were adequate serum levels detected (Plachouras et al. 2009).

Reported nephrotoxicity ranges between 8 and 36%. Factors associated with nephrotoxicity are hypertension, chronic renal insufficiency, diabetes mellitus and use of aminoglycosides (Montero et al. 2009). Reported neurotoxicity ranges between 7 and 29%, with oral and perioral paresthesias, visual disturbances and polyneuropathy; respiratory apnea is rare (El Solh and Alhajhusain 2009).

Experience with parenteral polymyxin B is limited. A report for 74 patients with nosocomial pneumonia by MDR *P. aeruginosa* disclosed favorable responses in 47.3%. Independent risk factors associated with unfavorable clinical outcome were the presence of ARDS (adult respiratory distress syndrome) and septic shock (Furtado et al. 2007).

Other Therapeutic Options

Other salvage options for the management of MDR *P. aeruginosa* are limited. Doripenem is a new carbapenem resistant to hydrolysis by renal dehydropeptidase I. Randomized clinical trials in patients with nosocomial pneumonia and VAP disclosed similar clinical efficacy to comparator agents piperacillin/tazobactam, imipenem and meropenem. Doripenem is more stable than the other carbapenems in dilution allowing its administration over a long infusion time. This may allow for a longer T>MIC compared with the other carbapenems and expectance of better clinical efficacy (Chastre et al. 2008; Matthews and Lancaster 2009).

Clarithromycin may be an adjuvant therapy for the management of VAP by XDR *P. aeruginosa*. In a double-blind, placebo-controlled trial 200 patients were randomized to either placebo or to clarithromycin. Selection of other antimicrobials was done by the attending physicians. One gram of clarithromycin was infused within 1 h through a central catheter, once daily for three consecutive days. XDR *P. aeruginosa* was the second most common cause of VAP. Administration of clarithromycin was accompanied by significant earlier resolution of VAP (median 10 days versus 15.5 days of the placebo group) and by significant reduction of OR for death by septic shock and multiple organ dysfunction (3.78 versus 19.00 of the placebo group). It is assumed that part of the efficacy of clarithromycin is mediated through the inhibition of quorum sensing of XDR *P. aeruginosa* (Giamarellos-Bourboulis et al. 2008).

A promising novel adjuvant therapy against MDR *P. aeruginosa* is the development of a monoclonal IgM antibody, named panomacumab, targeting O11 isolates. Its safety was assessed in an open-phase II trial in 18 patients. Despite the limited number of enrolled patients, mortality was lower that predicted (Lu et al. 2009).

Containment of MDR Isolates

Containment of MDR isolates of *P. aeruginosa* is mainly based on diverse techniques. The most popular of them are antibiotic cycling, attempts to limit cross-transmission and efforts to prevent colonization of the digestive tract.

Antibiotic Cycling

This strategy is based on epidemiological data clearly showing that (1) the main driver to the acquisition of resistant carriers is the selection pressure by prior extensive use of antimicrobials in the environment; and (2) acquisition of resistance to an antimicrobial belonging to a certain class is probably accompanied by resistance to all members of that class. As a consequence, to maintain a class of antimicrobials active against a certain bacterial species, that species should not be exposed to that class for a certain period of time. To achieve that, the concept of cycling of empirically prescribed antimicrobials has been developed. According to that strategy, two or more classes of antimicrobials are selected to be administered as empirical treatment of nosocomial infections in environments with a high MDR rate. The selection of antimicrobials is based on surveillance cultures before the implementation of that strategy. Each antimicrobial class is empirically prescribed for a certain period of time ranging between 2 and 4 months followed by the second and third class for the same period. Then these cycles rotate. The efficacy of that strategy is monitored by surveillance cultures, by the advent of infections by MDR isolates and by the resistance phenotypes of the isolates to rotating antibiotics (Kollef 2006).

It is questionable if the implementation of this strategy does indeed limit the emergence of MDR *P. aeruginosa*. Cumulative evidence derived from prospective clinical studies is described in Table 2. Despite the controversial findings of these studies, it is obvious that the implementation of such a strategy has a great impact on the prescription habits of physicians (Merz et al. 2004). In any case, the lack of uniformity of the results of trials about the efficacy of the antibiotic cycling strategy to limit colonization of patients by MDR *P. aeruginosa*, indicates that this strategy is one available measure to control the spread of MDR isolates but it is not the ultimate solution to the problem.

Limitation of Cross-transmission

There is not adequate evidence, as created by randomized clinical trials, that the application of widely described infection control and prevention measures can limit cross-transmission of MDR *P. aeruginosa* (Harris et al. 2006). The most widely known is to perform surveillance cultures in environments where these isolates emerge and particularly in the ICU. These cultures should be performed upon patient admission and at regular time intervals e.g. once weekly. They consist of tak-

Table 2 Results of clinical trials of antibiotic cycling strategies on the acquisition of multidrug-resistant *Pseudomonas aeruginosa* colonizers

Reference	Cycles	Implementation (number of patients)	Comparison (number of patients)	Outcome
Cadena et al. 2007	Cefepime 3 mo; Pip/tazo 3 mo; × 5 years	Hematology/oncology unit	TICU	• ↑ susceptibility to cefepime (OR: 4.27) • ↑ susceptibility to pip/tazo (OR: 4.61)
Martinez et al. 2006	Cefepime/ceftazidime 1 mo; Ciprofloxacin 1 mo; Carbapenem/pip/tazo 1 mo	ICU (n = 167)	Another ICU (n = 179) with mixing habits	• ↓ acquisition of MDR *P. aeruginosa* (5% vs 11%)
Van Loon et al. 2005	Levofloxacin×4 mo; Cefpirome×4 mo; Levofloxacin×4 mo; Pip/tazo×4 mo	ICU (n = 341)	None	• ↓ exogenous acquisition of *P. aeruginosa*
Warren et al. 2004	Cefepime 3 mo; FQ 3 mo; Carbapenem 3 mo; Pip/tazo 3 mo × 2 rotations	ICU (n = 930)	Baseline (n = 242)	• No effect on mortality • ↑ length of ICU stay • No effect on rectal colonization by MDR *P. aeruginosa*

MDR multidrug-resistant, *OR* odds ratio, *FQ* fluoroquinolones, *ICU* intensive care unit, *TICU* transplant intensive care unit

ing samples of flora of the gastrointestinal tract, of the upper airways, of tracheobronchial secretions and of urine for culture. Samples of flora of the gastrointestinal tract and of the upper airways are taken by swabs from nares, pharynx and rectum. Once surveillance cultures indicate the acquisition of MDR *P. aeruginosa* the patient should be isolated. Whether this is feasible or not, the patient should be treated with caution. Disposable gloves, masks, drapes and gowns should be placed in a wheel table close to the bed. Each nurse and physician should wear them before handling the patient and dispose of them at the end of the task. Antiseptic hand hygiene should be used before and at the end of the task. A surveillance nurse can help considerably.

When an outbreak supervenes, this should be recognized early by the ICU staff. The staff should be alerted when the incidence of infections by MDR *P. aeruginosa* increases abruptly within a brief time period. In these cases, it is mandatory to recognize early the source of the infection. This necessitates cultures of both biological samples as those defined above but also of the environment. The latter include tap water, sinks, walls, bed rails, monitors and endoscopes. PFGE electrophoresis of the isolates showing the different genotypes may help considerably since the isolate with the most frequent pulsetype is the culprit of the outbreak. Once the source of infection is disclosed, which is often somewhere in the environment, thorough disinfection should be undertaken. This should be followed by the isolation measures mentioned above (Aumeran et al. 2007; Rogues et al. 2007).

Preventive Strategies

Two measures have been described as promising to prevent colonization of ICU patients by MDR *P. aeruginosa*; oral intake of probiotics and selective digestive decontamination (SDD).

In a recent clinical study, 208 patients admitted in the ICU were randomly assigned to daily intake of placebo (n = 106) or 10^9 colony-forming units of *Lactobacillus casei rhamnosus* (n = 102) from the third day after admission until discharge or death. Results revealed a significant time delay of patients administered probiotics to colonization of tracheobronchial secretions by *P. aeruginosa* (median 50 days) compared with the placebo group (median 11 days) (Forestier et al. 2008).

In a recent multicenter clinical trial in 13 ICUs, de Smet et al. (2009) randomized patients upon admission to either standard care (n = 1,990) or selective oral decontamination (SOD, n = 1,904) or SDD (n = 2,045). SOD consisted of the topical application in the oropharynx of tobramycin, colistin and amphotericin B for four consecutive days. SDD consisted of the intravenous administration of cefotaxime and of the topical application in the oropharynx and in the stomach of tobramycin, colistin and amphotericin B for 4 consecutive days. Surveillance cultures revealed the isolation from the respiratory secretions of ceftazidime-resistant *P. aeruginosa* in 3.5, 1.1 and 0.4% of patients respectively; and of ciprofloxacin-resistant isolates of 3.7, 1.8 and 0.9% of patients respectively.

Conclusions

Analysis of the epidemiological factors affecting acquisition of MDR *P. aeruginosa* clearly shows that the main driver creating the emerging problem of resistance is the over-consumption of antimicrobials. The proposed strategies for containment of these isolates like antibiotic cycling and limitation of cross-transmission will help only when all physicians realize that the emergence of MDR isolates and the enormous mortality they cause have their origins in the inappropriate administration of wide spectrum antimicrobials. Only when all physicians adapt to that rationale, will the perspective of containment of MDR *P. aeruginosa* be a possibility.

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Multidrug-Resistant Infections in Low-Resource Health Care Settings

Cara Winters and Hellen Gelband

Abstract The confluence of a high burden of infections, overcrowded conditions, poor hygiene, and lack of access to newer antibiotics in large, urban, public hospitals in poor countries is leading to higher reported levels of antibiotic resistance. Most resistance data come from the sickest patients and those who do not respond to any antibiotics; therefore, reported rates may overstate the problem. Nevertheless, it is evident that lack of diagnostic and other microbiologic resources encourage overtreatment and contribute to mistreatment in hospitals. High national death rates from childhood pneumonia in the community indicate a lack of access and underuse. Hospital-acquired infections (HAIs) impose significant health costs in poor countries where people pay for health care out of pocket. Patients, especially neonates, are more likely to die for lack of effective treatment and are likely to be ill and infectious for longer, hence more likely to spread resistant organisms. Underused but highly cost-effective interventions include vaccination to reduce disease burden (benefiting the entire population, not just hospitals), improved hospital infection control (which can be relatively inexpensive), and changing incentives toward more appropriate antibiotic use.

Keywords Antibiotic resistance • Stewardship • Pneumonia • Microbiology laboratories • Pharmacy • Prescriptions

In low-resource settings, particularly in public hospitals and poor countries—the conditions that allow infection to spread easily are common: overcrowding, poor hygiene, and frequent inadequate treatment. It is almost a given that in such settings the rates of hospital-acquired infections (HAIs) are not monitored. Because of poor microbiology services, rates of antibiotic resistance are not known. Reports of high rates of both HAIs and antibiotic resistance are common but may not be reliable, and it may be that the reports are based on patients with hard-to-treat resistant infections and therefore overstate the problem.

In contrast, in private hospitals that serve better-off patients, newer and more expensive antibiotics are likely to be available and microbiology laboratories' func-

H. Gelband (✉)
Center for Disease Dynamics, Economics and Policy, 1616 P Street, NW, Suite 600
Washington, DC 20036, USA
e-mail: gelband@cddep.org

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_12,

tion, hygiene, and overall conditions are often better. However, no assumptions about HAI or antibiotic resistance rates should be made without evidence. In some US hospitals, antibiotics may "substitute" for infection control and it is unlikely to be of the highest standard (Laxminarayan and Malani 2007). There is substantial scope for improvement in both public and private hospitals.

This chapter will discuss infections acquired in hospitals and other health care facilities, but these institutions do not exist in a vacuum. The infectious disease profile of the community is merely reflected in the hospital patient population. In fact, both public and private hospitals demonstrate the twin issues of HAIs and antibiotic resistance in low-resource countries. Hospitals all over the world have similar structures: they perform surgery, have similar departments representing the same health care professions, and have a recognizable authority structure. The major diseases may be somewhat different, but still fall into recognizable categories. Even where antibiotics are available without prescription and seem to be widely used in the community, it may be that hospital patients consume more antibiotics per capita than people in the community at large. Inadequate infection control and excessive antibiotic use in hospitals has spillover effects in the community, as well as in other health care institutions (Smith et al. 2005). But it is the characteristics of the hospitals themselves, as institutions with control mechanisms, hierarchical structure, and standard units—that make HAI reduction and promotion of rational antibiotic use a reasonable goal.

Burden of Infection in Low-Resource Settings

The burden of infectious diseases is generally high in developing countries, and antibiotic resistance affects treatment of all illnesses caused by bacterial infection. Of the 8.8 million deaths in children under the age of 5 years, infectious diseases account for 5.5 million (63%), with 2 million (20%) alone due to acute respiratory infections (ARIs), the leading cause of infant mortality (WHO 2009b). Most of these deaths occur in developing countries. Other vulnerable groups are also affected disproportionately in low-resource countries, including immuno-compromised individuals and the very poor, who live in substandard conditions and often lack fresh water and sanitation (WHO 2009a). Although projections of disability-adjusted life years (DALYs) for the year 2020 anticipate large health improvements in developing countries (Hart and Kariuki 1998; WHO 2009a), they fail to account for the development of antibiotic resistance in the following infectious diseases:

- *Neonatal sepsis.* More than 40% of the estimated 10.8 million deaths in children annually occur in young infants, and 99% of these deaths are in low and middle-income countries (Newton and English 2007). Severe infections are a direct cause of 26% of these deaths globally, with bacteremia responsible for at least one-third of infant mortality in some areas (Berkley et al. 2005; Newton and English 2007).

- *Acute respiratory infections.* ARIs are the leading cause of morbidity and mortality worldwide. Pneumonia accounts for the majority of ARI deaths in children under 5 years of age and causes 20% of all mortality in young children in developing countries (Rudan et al. 2008; Frist and Sezibera 2009). *Streptococcus pneumoniae* is the main bacterial cause of pneumonia and other pneumococcal diseases, resulting in 70% of all ARIs. These infections can complicate other serious conditions, especially in young children. Pneumonia is the commonest cause of death among people with AIDS.
- *Diarrhea.* More than 3 billion episodes of diarrhea occur each year, causing an estimated 1.5–2 million deaths (HaRP 2009). Although most diarrheal episodes are self-limiting and can be treated with oral rehydration solution, antibiotic resistance precipitates therapeutic failure in cases where antibiotic treatment is necessary. In Africa, for instance, non-typhi *Salmonella* (NTS) are among the most important causes of bloodstream infections in children under the age of 5 years and in some countries are second in importance only to invasive pneumonia as a cause of bacteremia (Kariuki et al. 2006).
- *Sexually transmitted infections.* Sexually transmitted infections (STIs) are common in developing countries and where AIDS is prevalent because the presence of an STI increases the probability of HIV transmission. Although gonorrhea, the most common STI, is treatable with antibiotics, controlling its spread has been compromised by the emergence and transmission of strains resistant to penicillin, tetracycline, and spectinomycin (Okeke et al. 2005a).

HAIs and Antibiotic Resistance in Low-Resource Settings

Hospital-acquired infections have been increasingly documented in developing countries over the past 25 years, including hospital transmission of community-acquired, multidrug-resistant organisms such as pneumococci, *Salmonella* spp, *Shigella* spp, and *Vibrio cholerae*. Most studies, however, use bacterial cultures from patients in tertiary hospitals (where microbiology facilities are more likely to exist) for which first-line antibiotics have failed, so the results probably overstate the levels of resistance in hospitals and certainly in the general population.

Overcrowding in hospital wards, inadequate staffing, and insufficient supplies hinder infection control practices, creating an environment where bacteria can easily spread within the hospital and eventually from hospital patients and staff to the community. The absence of (or lack of adherence to) infection control guidelines in clinical settings also means that hospital staff may not follow basic procedures, such as hand washing and equipment sterilization. The transmission of highly pathogenic and drug-resistant bacteria within the hospital serves to amplify the problem of drug resistance in developing countries by increasing mortality and morbidity as well as treatment costs to the patient and health care system (Bartoloni and Gotuzzo 2010; Franco-Paredes and Santos-Preciado 2010).

Consequences of Antibiotic Resistance in Developing Countries

The rise in bacteria resistant to first-line antibiotics and the expense of newer second and third line drugs present a public health challenge with serious implications for the well-being of populations living in developing countries. The rate of the introduction of new antibiotics has slowed relative to the rate of development during the 1950–1970 period, but under current conditions, it will be many years before the new drugs become available and affordable in poor countries. The loss of the drugs that once cheaply and quickly treated common infections contributes to prolonged hospitalization and more complicated illnesses, leading to higher morbidity, mortality, transmission, and health care expenses. For the infected patients, disease caused by antibiotic-resistant pathogens can mean more virulent infections, requiring repeated doctor visits, hospital admissions, prolonged care, and personal financial drain. If the initial therapy is inappropriate or ineffective, the risk of mortality increases.

Within the hospital, well patients, visitors, and personnel can spread bacteria; and though not infected themselves, they can spread disease in the hospital and into the community. Procuring and stocking expensive second line agents, ordering costly diagnostic tests, and increasing demand for hospital bed space and personnel time are especially pressing for fragile health systems already facing considerable resource constraints.

Studies in developed countries have evaluated the impact of resistance on the affected patient by assessing mortality rates, length of hospital stay, and hospital charges (Cosgrove and Carmeli 2003). Resistant infections (compared with susceptible bacteria) increase the chance of dying and costs of hospitalization by 1.3–2-fold (Cosgrove and Carmeli 2003). For example, patients infected with extended-spectrum b-lactamase (ESBL) producing strains of antibiotic-resistant *Escherichia coli* and *Klebsiella pneumoniae* were in the hospital for a median of 11 days, as compared with 7 days for people with susceptible strains of those bacteria (1.76 times greater, $p=0.01$), had hospital charges that were nearly three times higher ($ 66,590 versus $ 22,231, $p<0.001$), and were effectively treated for their infection significantly later (72 h after infection suspected versus 11.5 h for controls, $p<0.001$) (Lautenbach et al. 2001; Slama 2008).

Two analyses of methicillin-resistant *Staphylococcus aureus* (MRSA) show similar results. In a meta-analysis of studies, MRSA infection was associated with a nearly twofold increase in mortality compared with susceptible *S. aureus* (OR 1.93; $p<0.001$) (Cosgrove et al. 2003). Infection with MRSA bacteria was also associated with longer hospitalization (1.29 times higher, $p=0.016$) and higher costs (1.39 times higher; $p=0.017$) (Cosgrove et al. 2005). Other patient outcomes needing further exploration include the long-term effects of having a resistant infection on future health and the loss of work hours associated with prolonged hospitalization and recovery time (Cosgrove and Carmeli 2003).

Studies set in developing countries that document the clinical outcomes of resistance and financial costs are extremely limited. Further, establishing the burden

of disease caused by bacterial organisms is a challenge because critical data are absent for most developing countries. Understanding of the societal consequences of antibiotic resistance is also limited, as it is for infectious diseases generally, because current estimates take into account only the direct effects on patients, not the wider effects on families, economies, and society at large. The information presented in this chapter provides a general picture of how bacterial disease affects the wellbeing of populations in low- and middle-income countries and confirms the consequent need for preserving effective treatment.

Health Implications

The following recent studies, all investigating bloodstream infections in neonates and children, for whom prompt treatment with an effective drug can be lifesaving—have reported a higher risk of death from infection with a resistant bacterium than from infection with a sensitive one. For Gram-positive bacteria, the resistant strains are MRSA, and for the Gram-negatives, they are ESBL producers.

- In Gaza City, Palestine, neonates infected with resistant *Acinetobacter baumannii* were more likely to die than those with sensitive strains (El-Astal 2004).
- In Bugando Medical Centre, Tanzania, neonates with all types of bacterial sepsis were studied, and those with either MRSA (among Gram-positive organisms) or ESBL-producers (among Gram-negative organisms) were much more likely to die than those with similar sensitive organisms (Kayange et al. 2010).
- In Dar es Salaam, neonates with ESBL-producing Gram-negative sepsis were almost twice as likely to die (71%) as those with otherwise similar sensitive Gram-negative infections (39%) (Blomberg et al. 2005).
- In Dar es Salaam, children (up to age seven) with bloodstream infections were at significantly greater risk of dying because they were treated with antibiotics that were ineffective against their resistant infections (Blomberg et al. 2007).
- In India, the case fatality rate was significantly higher among neonates with ESBL-producing bacteria (>60%) than in those with sensitive Gram-negative bacteria (36%) (Jain et al. 2003).

We have been unable to locate similar studies in high-income countries, presumably because deaths from neonatal sepsis are rare and are unlikely to be due to drug resistance. In general, tests to determine the susceptibility profile of the infecting organism would be conducted early, and an appropriate antibiotic would be used.

Treatment Delays and Failure

Antibiotic resistance is a growing problem in illnesses that account for the majority of the developing world's infectious disease burden. When drugs are no longer effective against common pathogens, the possibilities of treating infectious diseases

are dramatically reduced, and the risks of treatment delays and failure multiply. In industrialized countries, many people (or their insurers) can afford expensive alternatives like vancomycin, but in developing countries, cost constraints prevent the application of newer agents (Okeke et al. 2005a). In national referral hospitals, the first-line antibiotics are mainly inexpensive options: penicillin, chloramphenicol, tetracycline, and cotrimoxazole (Okeke et al. 2005b). Cefuroxime, amoxicillin-clavulanate, and ciprofloxacin may be used as second-line agents in patients with the means to pay for additional treatment. In district hospitals and dispensaries, typically only first-line agents are available, and even these are sometimes not stocked (EPN 2010). Thus, there is more potential for adverse effects of antibiotic resistance in the developing world, where more of the population suffers from bacterial illness and second-line therapies for drug-resistant pathogens are unavailable to most people.

A related problem is that clinicians in developing countries tend to diagnose and prescribe medication empirically. People with undetected resistance then receive antibiotics to which their isolate is not susceptible. For example, one study in western Kenya found that more than half of the patients treated empirically for bacterial diarrhea were given ineffective antibiotics. Among patients with shigella, this number exceeded 80% (Shapiro et al. 2001). Ineffective treatment does not just create a false sense of security for patients and health care workers; it also delays the time until appropriate therapeutic action is provided. Several studies have shown that delays in appropriate therapy are associated with adverse outcomes (Cosgrove and Carmeli 2003). In one report, patients infected with ESBL-producing strains of *K. pneumoniae* and *E. coli* were effectively treated more than 60 h later than counterparts with susceptible infections, leading to significantly longer hospitalizations and higher hospital charges.

Enhanced Virulence

Antibiotic resistance can affect patient outcomes in other ways as well, such as if the pathogen is virulent and causes more complicated and deadly infections (Cosgrove and Carmeli 2003). The relationship between resistance and virulence can vary depending on the organism, the type of antibiotic, and the mechanism of resistance. In situations when mutations lead to reduced "fitness" of the bacterium, compensatory mutations can arise. Currently there are no studies demonstrating a correlation between increased fitness in organisms with resistance mutations and adverse clinical outcomes, but it remains a concern among researchers in the field.

Economic Implications for Hospitals and Society

Drug resistance can necessitate longer hospital stays, more expensive second-line agents, and more extensive diagnostic procedures. Including the costs of lost work

hours or premature death, the additional costs associated with antibiotic resistance place a considerable burden on the patient and family, the hospital, and the public health system. Although the exact costs imposed on society by antibiotic resistance are unknown, estimates range from $ 350 million to 35 billion (Laxminarayan 2001), depending on whether the costs of deaths are considered. Information from the United States suggests that longer hospital stays and increased intensive care unit admissions for patients with resistant infections cost $ 4 billion to 7 billion a year (REACT 2008). The cost of containing an outbreak of a resistant organism such as VRE or MRSA within a hospital can also be high and reach millions of dollars (Smith and Coast 2002). Studies aimed at measuring the excess costs of treating patients infected with resistant organisms typically focus on expenses associated with control of the pathogen in the hospital or therapeutic management of the patient, longer hospital stays, supplementary investigations with lab tests and x-rays, and increased spending on additional or alternative treatments with newer, more expensive second or third-line antibiotic agents (Howard 2004). Mauldin et al. (2010) recently investigated the hospital cost and length of stay attributable to Gram-negative drug-resistant HAIs in a U.S. hospital and they found that the total hospital cost increased 30% ($p<0.0001$) and the length of stay rose by 24% ($p=0.0003$), compared with hospitalizations caused by susceptible strains. The result was a median total cost of $ 38,121 higher for patients infected with resistant bacteria.

Data on the prevalence of bacterial disease and resistance in developing countries is limited and assessing the exact costs incurred by antibiotic resistance is difficult, given the unknown impacts of the underlying disease. Consequently, most studies originate from countries with extensive data and sophisticated health care systems. Research also fails to account for lost work hours and productivity and the consequences on other forms of health care, including advanced surgical procedures that depend on antibiotic prophylaxis. Thus, what information does exist is incomplete, and the economic effect of resistance on families and society remains to be fully assessed.

The loss of cheap antibiotics increases the economic burden on institutions struggling to purchase even basic, essential medicines. In developing countries, antibiotics are a scarce resource, and most clinics and hospitals can barely afford common first-line agents, much less second and third-line alternatives. Where newer agents do exist, the prohibitive cost of these drugs places them beyond the reach of most patients, many of whom pay out of pocket for the drugs and other consumables used in the hospital. This dynamic forces clinicians and national health officials to choose between spending more money on higher cost drugs or continuing to use ineffective but cheap antibiotics with a possible risk of increased morbidity and mortality. Forster (2010) has articulated the ways in which costs associated with this trade-off can be conceptualized: the actual amount paid for a drug plus its “opportunity cost,” the value of a forgone alternative. Considering financial costs alone, variation in prices of antibiotics is considerable. The wholesale price differential between amoxicillin and co-amoxiclav, for example, is on the order of a factor of 20 (Forster 2010). This means that where resistant bacteria necessitate the use of co-amoxiclav, only 5% of the patients can be treated for the same budget as with amoxicillin.

Resistance also leads to the use of ineffective antibiotics, wasting funds without treating the patient, and in settings where clinicians are concerned about resistance, a switch to newer antibiotics when an older one is still effective, wasting the excess cost of the new drug. For instance, if resistance to first-line agents prompts a clinician to substitute treatment with co-amoxiclav when the bacteria of a particular infection remain susceptible to amoxicillin, the opportunity cost of the drug is nearly $ 8 per patient, without considering the opportunity cost of future resistance to the new therapy. This is of particular concern in countries where laboratory diagnostics are not frequently used and drugs are prescribed empirically. In Thailand, only 9% of antibiotics administered in a teaching hospital were appropriate to the patient's condition, and 36% of patients were given antibiotics without evidence of an infection (Aswapokee et al. 1990). In Papua, New Guinea, chloramphenicol resistance and the risks of chloramphenicol treatment have grown unacceptably high, prompting a switch to ceftriaxone as a safer but more expensive option (Forster 2010). The cost of this switch was roughly $ 13 per patient: $ 3.29 for chloramphenicol treatment versus $ 16.20 for ceftriaxone. If antibiotic sensitivity tests were available, clinicians might switch back to chloramphenicol on a case-by-case basis, saving money for both the patient and the health care system.

The costs related to antibiotic substitution vary with context. When patients lack insurance and drug availability is limited and typically decided through an essential drug list, demand for older drugs in formal health care settings remains relatively inelastic, regardless of resistance (Howard 2004). On the other hand, the unregulated sale of antibiotics without prescriptions results in a more flexible demand for newer agents and increased substitution costs relative to treatment failure.

Ultimately, treatment delays and failure (in cases where alternative therapies are unavailable or unaffordable) raise costs, as does the substitution of newer agents where these drugs can be freely prescribed and purchased. A study of pneumonia in Iceland found that infections caused by penicillin-resistant strains necessitated more expensive treatment ($ 736 for the resistant strain versus $ 213 for susceptible infections) as well as longer hospital stays (26.8 days versus 11.5 days) (Einarsson et al. 1998; REACT 2008). In coastal Kenya, resistance to chloramphenicol, amoxicillin, cotrimoxazole, and gentamicin in Gram-negative sepsis is common, and susceptibility remains only to two rarely used drugs, ciprofloxacin and cefotaxime. The cost of treating a 15 kg child with sepsis would be $ 0.38–2.30 for gentamicin and chloramphenicol versus $ 73–108 for the effective drugs (Bejon et al. 2005). A similar situation exists for drug-resistant *Haemophilus influenzae* type b in children living in the same area (Scott et al. 2005). In places with per capita incomes of $ 400–1,500 a year, costs like these can lead to a cycle of noncompliance, poor clinical outcomes, and financial ruin as untreated infections spread from the hospital and through the community (Mir and Zaidi 2010).

The process of switching therapies is yet another cost associated with the loss of antibiotic effectiveness in developing countries (Forster 2010). Logistical challenges involved in switching therapies include training health care workers, revising guidelines and essential drug lists, and altering national stock levels so that the new drug is available in pharmacies and health facilities when the treatment is launched

(Goodman et al. 2001). Further, it is difficult to employ cost-benefit calculations when deciding on a course of action because of disparities in accounting for costs when assessing treatment delays and failure. For example, delays and failure costs borne by society, such as the transmissibility of untreated disease and the extent to which the use of a new drug will reduce its future efficacy, are usually not included when health authorities assess whether the costs of failure of older, cheaper drugs are outweighed by the benefits of an expensive new alternative.

The Association of Poverty and Antibiotic Resistance

Conditions associated with poverty in developing countries exacerbate the risks of resistance, even though the poor contribute less to the problem of selective pressure than do the better off (Okeke et al. 2007). Inadequate hygiene and sanitation, unreliable water supplies, and malnutrition in developing countries increase the rates of bacterial infection and promote transmission of resistant pathogens (Laxminarayan 2002). People living in poor countries are less likely to have access to health care and essential drugs, including basic antibiotics, and therefore are more vulnerable to the consequences of resistance (Okeke et al. 2007). Some pathogens, such as NTS, even produce different syndromes in low and high income patients. Whereas NTS infection is typically associated with gastroenteritis in wealthier patients, in Kenya, NTS are predominant causes of life threatening bacteremia in infants and children living in slums (Berkley et al. 2005; Kariuki et al. 2006; Okeke et al. 2007). Because gastroenteritis is self-limiting but bacteremia requires prompt antibiotic therapy, access to effective antibiotics is crucial. The emergence and spread of resistant organisms mean that even if treated, these children often cannot be cured.

Factors Determining Antibiotic Use in Hospital Settings

Antibiotic resistance emerges in part from antibiotic use and the selection pressure it places on bacteria. Misuse and sub-optimal consumption of antibiotics, including under and overdosing the correct drug for an infection or inappropriately prescribing antibiotics for viral or nonbacterial diseases are complex problems involving regulators, clinicians, patients, and health care administrators. Furthermore, in many developing countries, antibiotic misuse is worsened by conditions of poverty. Poor health care services and unreliable access to medicines are common problems. From reports on antibiotic prescribing patterns, we know that health facilities often provide medicines that are not indicated for particular infections or prescribe insufficient regimens of correct drug choices.

In Kenya, a general assessment of inpatient pediatric care in all district hospitals revealed that case management was frequently not in line with national or international guidelines, and prescribed doses of common parenteral antibiotics were

often too high (chloramphenicol) or too low (gentamicin) for respiratory tract infections (English et al. 2004). Musoke and Revathi (2000) observed that prolonged (73%) and sometimes unjustified (42%) use of antibiotics in the neonatal unit of the Kenyan national referral hospital contributed to increased antibiotic resistance in hospital-acquired infections. Approximately one-third of all patients admitted to the unit were prescribed antibiotics, and less than half of those patients were evaluated with laboratory tests to determine the infecting organisms or to confirm drug susceptibility. Even in the country's national referral hospital, all sick newborns were presumed infected until proven otherwise, leading to indiscriminate, prolonged, and inappropriate use of antibiotics.

Optimal antibiotic use can be promoted by altering behavioral incentives such that individuals consider the wider costs of consuming these drugs (Laxminarayan 2002). Viewed as a behavioral issue, inappropriate antibiotic use and resistance stem from misaligned economic incentives and other social factors (Laxminarayan 2003a). Weak management and inadequate regulation lead to the indiscriminate use of antibiotics in hospitals and health care centers. Additionally, the lack of diagnostic systems and lab facilities encourages empiric prescribing of antibiotics if the bacterial etiology of a disease is undetermined and different conditions manifest with similar symptoms.

The literature on determinants of antibiotic use is limited and sometimes conflicting. For example, some analysts believe that deficiencies in clinicians' education are a prime cause of irrational prescribing, but others demonstrate that antibiotics are misused even when clinicians appear to have correct knowledge. The factors that influence antibiotic use in health care settings, particularly the perceptions and motivations of prescribers and consumers and their responsiveness to behavior change interventions, are not well understood. The problem requires more research attention to the design and implementation of successful policies that curb resistance.

The remainder of this section explores factors leading to inappropriate antibiotic use in hospitals.

Economic Incentives

Many questions exist about what motivates antibiotic prescribing and whether it responds to alterations in economic incentives. Although externalities and free riding are frequently discussed in theory, few investigators have studied how hospital financing systems and profits from antibiotic sales create incentives to use antibiotics or how insurance coverage motivates patient demand. Financing is a particular concern in countries that rely on cost-sharing or revolving drug funds to generate revenue, since both have the potential to create incentives that lead to over-prescribing while raising barriers to care for low income patients. Data on the supply and demand responses to antibiotic prices and payment mechanisms (insurance, credit, and exemption schemes) available to consumers are typically not available for de-

veloping countries. Information on clinicians' response to consumers' perceptions about the relationship between quality of care and treatment expense is also lacking, particularly whether low-cost remedies are perceived as inferior to time-consuming and expensive consultation or hospital admittance.

Externalities and Clinician Prescribing

Antibiotic effectiveness can be viewed as a shared resource in which current use depletes future value and imposes costs on society in the form of longer hospitalization, higher mortality rates, and the diversion of resources into the provision of newer and more expensive drugs. In making treatment decisions, prescribers should weigh the favorable effects of applying antibiotics to improve a patient's health against the negative consequences for the public and future drug effectiveness (Laxminarayan 2003b). However, clinicians usually ignore the future therapeutic risks to society associated with antibiotic use and instead focus on the direct benefits of antibiotic treatment to their patients. Although there is evidence that indicates patients with a history of recent antibiotic use are at greater risk for drug-resistant infections, the unwanted and indirect effects of antibiotic use are typically not felt by the consumer or supplier of treatment (Laxminarayan et al. 2005). The externalities mainly affect those outside the prescriber-patient relationship and are consequent to the treatment (Smith and Coast 1998; Group 2008; REACT 2008). The use of co-trimoxazole prophylaxis in HIV patients is a prime example. Leaving issues of resistance unresolved, the World Health Organization (WHO) recommended in 2005 that all people with HIV receive co-trimoxazole prophylaxis. Countries receiving funds for HIV/AIDS from international donors have therefore added daily co-trimoxazole as part of regular HIV management. Resistance to this cheap and well-tolerated drug has since been documented in *S. pneumoniae* (Madhi et al. 2000; Pemba et al. 2008). Other pathogens that may become resistant with co-trimoxazole exposure include *S. aureus*, *Haemophilus influenzae* type b, *Shigella* spp, and *Salmonella* spp (Forster 2010). One set of particular benefits may thus be offset by a set of costs to public health. Complicating matters further, the exact relationship between current use and future resistance levels is unknown and rests on whether an antibiotic would regain effectiveness if temporally removed from active application (Howard 2004; Laxminarayan 2001). Scientists continue to explore whether resistance persists in an environment without antibiotics.

Hospital Infection Control and Free Riding

The development of antibiotic resistance within health care facilities is of particular concern. High selective pressure on bacteria from constant antibiotic use in a susceptible population leads to more rapid development of resistance genes and DNA transfer in the hospital (Mir and Zaidi 2010). As potential breeding grounds for the evolution of pathogenic, resistant bacteria and their subsequent spread to other

patients, health care staff and hospitals must implement infection control practices as fundamental aspects of quality health care (Franco-Paredes and Santos-Preciado 2010; Mir and Zaidi 2010). Unfortunately, the frequently overcrowded and under-resourced hospitals in the developing world have inadequate infection control measures and infrastructure. WHO estimates that 10–30% of all hospital admissions in resource-poor settings result in infection. The situation places health care workers and their patients at risk, and the transmission of drug-resistant bacteria within hospitals and into communities escalates the development and spread of resistance, increasing the need for antibiotic treatment.

The failure to establish sound infection control is partly due to reliance on antibiotics as a low-cost prophylactic alternative in high-risk hospital departments like the ICU, surgical wards, and neonatal units. In some instances, treating HAIs with antibiotics rather than preventing them is viewed as the cheaper method of addressing hospital infections. In industrialized countries, hospitals affected by resistant infections absorb some of the treatment costs and preventing the infection is usually more economical (Laxminarayan et al. 2005). In developing country facilities, however, resistant infections acquired in the hospital are not identified as such and patients incur nearly all the costs of treatment and prolonged hospital stay. With the financial burden of prophylactic antibiotic use or HAI treatment on the patient, the hospital is further incentivized to shift away from infection control practices underwritten by the facility.

Hospitals are especially likely to substitute antibiotics for infection control when they share patients with other facilities, as is the case in many developing countries' referral systems. In such a context, a person colonized with resistant bacteria in one hospital may introduce or increase the prevalence of the pathogen in a referral facility, and so on up the referral chain (Laxminarayan et al. 2005). If the number of admitted patients colonized with resistant bacteria is assumed to be low, a hospital will conduct some amount of infection control, since it will be relatively inexpensive to prevent the spread of the organisms. The value of infection control dramatically diminishes, however, as an increasing number of colonized patients are admitted and measures become more expensive and ineffective.

Non-Economic Incentives

Clinician Prescribing

Health care workers' level of knowledge and fear of negative outcomes, combined with the availability of diagnostic services and drug supply, influence antibiotic prescribing. A few studies have examined the extent of dispensers' knowledge and the provision of antibiotics in practice. In many developing countries, clinicians' knowledge may not be adequate. In a survey in Kenya about treatment for watery diarrhea, 71% of clinicians incorrectly cited antibiotics as among the most effective treatments, and 73% reported that antibiotics kill the viruses causing diarrhea (Ram

2008). In response to this problem, education interventions have been implemented by civil society organizations and ministries of health, in the belief that better diagnostic and therapeutic knowledge will lead to more appropriate antibiotic use. The reality, however, is more complex. Although the clinicians surveyed were consistent in their hypothetical recommendations for treating watery diarrhea, considerable variation existed in how they treated their most recent cases (Ram 2008). According to their statements, only 12% of health workers would prescribe antibiotics alone, but in practice this number was 20%. None of the knowledge parameters used by the researchers were statistically associated with treatment choices made by health care workers in either rural or urban settings.

Other influences appear to drive dispensing by even well informed practitioners. Inadequate diagnostics can lead to uncertainty about the best method of treatment and a fear of bad outcomes if antibiotics are withheld, particularly in areas of the world where the clinical manifestations of prevalent diseases overlap, as with malaria and pneumonia, and bacteremia and meningitis (Berkley et al. 2005). This can lead not only to overprovision of antibiotics in general, but also to heavy reliance on broad-spectrum drugs that promise to address a wide range of potential pathogens. One study highlights this problem in relation to limited diagnostics and pneumonia infections in malarial areas (Phillips-Howard et al. 2003). Because of the overlap in the clinical presentation of malaria and respiratory illness, penicillin was given as a safeguard treatment for possible pneumonia in 22% of children with a sole diagnosis of malaria. The risks of not treating a potential pneumonia infection were felt by clinicians to be far greater than the unjustified antibiotic use.

Empiric treatment of infectious diseases adds to the misuse of antibiotics and emerging resistance burden. Frequently, antibiotics are administered to patients without a lab confirmation of the infection or determination of antibiotic sensitivity patterns (Kakai and Wamola 2002). Additionally, data on local causes of infection and prevailing susceptibility patterns are generally lacking, leaving clinicians to operate in the absence of critical guidelines and diagnostic tools. Difficulty in determining the etiology of infection not only results in the misuse of antibiotics for viral infections, but also drives the unnecessary application of broad-spectrum agents (Mitema and Kikuvi 2004; Amábile-Cuevas 2010; Haak and Radyowijati 2010). With adequate diagnostics, clinicians could prescribe more narrow-spectrum antibiotics and help reduce selective pressure (Okeke et al. 2007). Instead, clinicians substitute bacterial identification and sensitivity testing with broad-spectrum antibiotics, which apply selective pressure on both the infectious pathogen and the larger population of normal flora in the patient (Amábile-Cuevas 2010).

Although missing lab services and diagnostics are regarded as drivers of irrational antibiotic prescribing, the availability of lab facilities and personnel does not necessarily mean that clinicians use them (Kakai and Wamola 2002; Haak and Radyowijati 2010). Hospital lab staffs often say they could help clinicians diagnose disease and rationalize drug use; clinicians assert that because the major bacterial diseases often lead to rapid death, especially among children, they cannot afford to wait for culture results before providing treatment. Studies on dispensers' behavior have not investigated what diseases clinicians feel confident about diagnosing and

treating without laboratory support and how they perceive the usefulness of laboratory diagnostics and antibiotic sensitivity tests to their practice. The long-term benefits of improved diagnostics are therefore unknown, as are the motivations for better use of lab services in routine clinical practice.

Even if clinicians are knowledgeable and diagnostics are readily available, effective treatment is impossible without a reliable supply of medicines. Clinicians in resource-poor areas must deal with chronic shortages of many remedies. The CDC study in Kenya found that a clinician's ability to provide the preferred treatment for childhood diarrhea (oral rehydration salts) was limited by a shortage of packets, leading to antibiotic use as an alternative. In Bangladesh and India, primary care facilities may prescribe antibiotics according to availability rather than the specific needs of the patient (Uppal et al. 1993; Guyon et al. 1994; Haak and Radyowijati 2010). When government stocks run dry, public facilities may start purchasing second-line antibiotics from private distributors, encouraging the development of resistance to an already limited supply of alternative treatments, and at a high direct cost.

Institutional Drivers of Antibiotic Use

Inadequate human resources, an absence of antibiotic use policies and infection control guidelines, low levels of data and surveillance, and ineffectual regulatory environments are critical issues in the spread of HAIs and escalating levels of resistant bacteria. Currently, most hospitals in the developing world have neither antibiotic use policies to inform empiric treatment, nor comprehensive infection control guidelines. Where these documents exist, hospitals tend to lack sufficient numbers of trained health care staff or the additional resources needed to communicate or enforce the guidelines. High levels of susceptible patients in an overcrowded and understaffed facility can overwhelm even a hospital dedicated to providing quality care. Basic hygienic equipment and supplies, such as soap and clean water, are often missing, and hospital management does generally not support infection control nurses or committees. In most hospitals, administrative support for rational antibiotic use is deficient, and in some, staff and consultant doctors are held to different antibiotic use standards, depending on the amount of revenue their practice yields for the hospital.

Surveillance and the ability to generate and use data to improve health care performance affect several aspects of antibiotic use. National surveillance systems that could produce data on HAIs and resistance patterns and enable better empirical treatment choices are largely absent and precluded by inadequate resources. A country's ability to select and procure medicines as part of its public health management requires epidemiological data on population morbidity, mortality, and in the case of antibiotics, susceptibility patterns across a range of drugs and pathogens. Successful infection control programs detect carrier patients and share HAI data to hospital staff, two actions shown to lower hospital infection rates even in the absence of specific interventions. Both however, are impossible without hospital surveillance.

Interventions

In hospitals and other health care settings in the developing world, interventions are the same as in wealthy countries: hospital infection control, particularly hand washing, and various hygienic guidelines and checklists.

These two classes of interventions (discussed in more detail below) generally have to do with the rational use of antibiotics and ways to reduce HAIs, not directly reducing the spread of resistant bacteria specifically. HAIs and resistance are closely linked. But because the hospital must respond to conditions in the community, preventing infection in the population at large will help hospitals reduce the demand for antibiotics and hence the spread of antibiotic resistance. Reducing the infectious disease burden through vaccines is paramount, and its role in developing countries should be recognized.

The underused vaccines that could have the biggest effect on antibiotic use in hospitals are against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. To these should be added one of the new vaccines against *Rotavirus*, the main cause of dehydrating diarrhea, which kills 400,000–500,000 infants and children in developing countries annually. Even though Rotavirus is, in fact, a virus, reducing its incidence will reduce antibiotic use. The most appropriate treatment for rotavirus and other causes of watery diarrhea is oral rehydration therapy, but since antibiotics are used inappropriately in many cases, reducing the number of cases will reduce antibiotic use.

There may well be other opportunities. Though the evidence comes from just a single study conducted in Bangladesh, seasonal influenza vaccine given to pregnant women averted about one-third of all cases of influenza and other respiratory illnesses in mothers and their infants up to 6 months of age (Zaman et al. 2008). Many of the respiratory illnesses, both bacterial and viral, would have been treated with antibiotics whether this was appropriate or not. If the finding turns out to be generalizable, the vaccine would prevent both dangerous illness in young mothers and babies and a common use of antibiotics.

These three briefly outlined approaches are worth exploring:

- Develop better quality diagnostics to help target antibiotic use. Using rapid diagnostic tests (RDTs) that would not require a microbiology laboratory could be a huge boon, although evidence of a positive effect of improved diagnostics on antibiotic prescribing patterns is currently lacking. An added benefit of better diagnosis, with either RDTs or enhanced laboratory capacity, is the potential for better surveillance of resistance trends.
- Address supply chain constraints and failures for existing drugs and improve patient access to trained prescribers and dispensers. Some incorrect patterns of use may relate directly to weaknesses in the drug supply chain or the accessibility of authorized prescribers.
- Use economic incentives such as subsidies to encourage better use of antibiotics. This strategy has been not well developed in any particular country but has great potential. Crafting interventions that create appropriate incentives and disincen-

tives for purchasers and sellers will require in-depth understanding of current incentives.

Each of these approaches may become more important as technologies develop and are more widely used around the world. For now, the main emphasis is rightly on infection control and guidelines and checklists.

Infection Control

In most low and middle-income countries no studies have been conducted on the effectiveness of infection control measures to reduce the spread of antibiotic resistance. Studies from wealthy countries are limited, but certain practices are considered effective. Increased hand washing and the use of alcohol rubs show consistent reductions in bacterial contamination (Thompson et al. 1982; Pittet et al. 2006; Lennell et al. 2008). The difficulty comes in getting hospital personnel to maintain the practice (Pittet et al. 2000).

For hospitals in developing countries, the challenges are many. For example, in an Indonesian pediatric intensive care unit, literal adoption of CDC guidelines was impossible because of several factors. They are: (1) poor physical environment such as absence of hand-washing basins and presence of contaminated tap water, (2) budgetary constraints, (3) unreliable and inappropriate supply of equipment and supplies, including reuse of single-use items, poor storage of reprocessed items, and overuse of expensive disinfection agents, (4) limited microbiologic diagnostic facilities, (5) lack of health care worker knowledge, particularly regarding transmission risks associated with poor practice, (6) local customs and culture, including the hierarchical relationship between physicians and nurses, (7) lack of institutional support from the hospital administration and infection control infrastructure, and (8) poor sterilization capabilities (Rhinehart et al. 1991 in Zimmerman 2007).

When the necessary elements of proper hygiene are in place, hand washing can work. In Argentina, an intervention combining staff education, performance feedback, and proper hand hygiene initiatives resulted in a decrease from 45.94 to 11.10 bloodstream infections per 1,000 intravascular device-days and from 47.55 to 27.93 HAI per 1,000 bed-days. Even though this initiative was in a well funded urban facility, barriers to implementation still existed, including lack of resources, infection control programs, awareness, and support (Rosenthal et al. 2003, 2005).

Beyond proper hand hygiene, the most commonly advocated approach in high-income countries involves identifying and isolating hospital patients who are colonized with certain bacteria (especially MRSA), and treating them separately from other patients. Studies of the effectiveness of this approach are sparse and contradictory. A systematic review of the efficacy of isolation found that, despite the limitations of existing research, isolation measures do appear to reduce transmission of MRSA (Cooper et al. 2005). The approach depends on being able to isolate the infected patients, which is not realistic in most large, urban, or public hospitals in low-resource countries.

An ongoing KEMRI-CDC study in Kenya is investigating the effect of various infection control interventions on the spread of health care-associated respiratory infections. Surveillance efforts through this activity will examine the effect of good hand hygiene measures on HAI trends. Information generated by this research will inform policy strategies concerned with infection control practices and their ability to reduce hospital disease transmission in a resource-constrained setting.

Guidelines and Checklists

Another approach that is gaining acceptance is the use of checklists and guidelines for standard hospital procedures. The biggest boost came from a trial conducted by a WHO patient safety initiative in eight hospitals around the world; (1) Amman, Jordan, (2) New Delhi, India, (3) Seattle, Washington, (4) Ifakara, Tanzania, (5) Manila, the Philippines, (6) Toronto, Canada, (7) London, England, and (8) Auckland, New Zealand (Haynes et al. 2009). These public and charity hospitals were very different, but the same checklist, which consisted mainly of common sense measures, was applied to surgery patients. Infection-related outcomes included surgical site infections, pneumonia, and death from all causes. The proportion of patients with surgical site infections and deaths were approximately cut in half, but there was no change in cases of pneumonia.

The WHO study is not the only one to report positive results with a checklist; Abbett et al. (2009) found a reduction in the incidence of *Clostridium difficile* attributable to a similar checklist. But even if guidelines and checklists promote good practice, they work only if followed. Adherence to guidelines can be stymied by patient demand for a particular treatment and by practitioners who do not understand the efficacy of the practice or lack awareness of the guidelines, resources and supplies, or motivation. In practice, infection control teams seem to make the difference between success and failure (Farr 2000; Larson et al. 2007), but whether they are necessary in all environments is unclear.

We found no information on how many hospitals in low-resource settings use checklists. From the ongoing Global Antibiotic Resistance Partnership, it is clear that few public or private hospitals in Kenya use checklists for infection control purposes or during clinical procedures. Although some private hospitals are reported to create and approve checklists, compliance is neither enforced nor well monitored. According to those working in infection control policy and drug resistance in the country, the issue is not developing the tool for an intervention but incentivising implementation and ensuring compliance (Ndegwa personal communication 2009; Revathi personal communication 2009).

Treatment guidelines matching conditions are standard features in many developing countries, but few have been evaluated for effectiveness (Le Grand et al. 1999). As with checklists, the mere existence of guidelines is not likely to have much effect. How they are introduced, publicized, disseminated, and applied is crucial. Where guidelines have been studied, evidence has been mixed. In Fiji, antibi-

otic use was reduced after standard treatment guidelines were introduced. A study in Uganda found that the introduction of national treatment guidelines and training did not decrease the number of antibiotics per patient, though compliance with the guidelines seemed to increase (suggesting improved treatment), with the most dramatic changes occurring among the least trained health workers (Naivalulevu 1990).

More recently in Bangladesh, 26 poorly performing centers were assigned a standardized intervention plus an audit, or nothing at all (control group). The results were as expected: in the guideline centers, antibiotic use declined by 7%, and in the group that was also audited, antibiotic use decreased about twice as much (Chowdhury et al. 2007). Of course, these results are short term only. A major challenge is maintaining or improving the rates of use of guidelines. The continued effort required is rare.

A great deal of effort goes into developing guidelines. In 2007, for example, the WHO India country office, the Indian Ministry of Health and Family Welfare, and the Armed Forces Medical College wrote national standard treatment guidelines. They were developed for 35 conditions with high prevalence in India. Different guidelines were created for each of four levels of care: solo physicians, health facilities with 6–10 beds, facilities with 30–100 beds, and facilities with more than 100 beds (WHO India 2007). This group of collaborators also estimated the cost of providing care as described in these guidelines. The guideline developers in this case (and in many other countries) considered what was known about antibiotic resistance.

The big question is how guidelines are best used. The science of developing guidelines is well established, but the science of implementing guidelines, like using checklists, is not. Both of these tools are clearly useful, and their implementation deserves more effort.

The authors were supported by the Global Antibiotic Resistance Partnership, funded by the Bill & Melinda Gates Foundation.

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Germ Shed Management in the United States

Kevin Outterson and Olga Yevtukhova

Abstract The US Medicare program reimburses only for discrete treatments of individuals with infections, but fails to pay for infection control or antibiotic stewardship more generally. By focusing solely on discrete hospitals and patients, Medicare ignores the larger epidemiological reality—that hospitals, nursing homes and other institutions operate within a germ shed. Under current Medicare rules, institutions that invest in infection control or antibiotic stewardship may actually lose money and benefit rival firms in the market. In effect, current Medicare rules subsidize MRSA pollution.

Keywords MRSA • HAI • Antibiotic stewardship • Medicare • Medicaid • Germ sheds

Germ Sheds

In the US, Medicare reimburses hospitals as if antibiotic resistance were localized only in the hospital itself. Medicare focuses on hospitals as discrete institutions, as if methicillin-resistant *Staphylococcus aureus* (MRSA) or other germs respected corporate boundaries on an organizational chart or legal boundaries on a map. US hospitals are paid by the case, but microbes operate in a larger epidemiological environment, a *germ shed*.

A germ shed is roughly analogous to a watershed: clinical regions that are epidemiologically interdependent and thus share positive and negative infectious disease externalities. For most hospitals, the germ shed will be larger than just the institution, but will also include long-term care facilities that transfer patients to and from the hospital. Other institutions in the germ shed could include ambulatory surgical centers, rehabilitation facilities, dialysis centers, prisons, schools and the community at large. The existence and scope of a germ shed is empirically established, using epidemiological data (Huang et al. 2010; Donker et al. 2010). Tools to promote the long-term effectiveness of antibiotics include infection control, vaccination, and antibiotic stewardship and other antibiotic conservation measures (Laxminarayan

K. Outterson (✉)
Boston University School of Law, 765 Commonwealth Avenue, 1140, Boston, MA 02215, USA
e-mail: mko@bu.edu

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_13,

and Malani 2007). Our primary insight is that some of these tools should be applied across the germ shed, not just in discrete institutions. This article will focus on MRSA as an example, but the principles may apply to other resistant pathogens.

This chapter explores the problems that US Medicare creates when it fails to modify reimbursement to account for germ sheds. One approach might reimburse regional groups of hospitals for infection control and pay bonuses for reducing infections within the germ shed. Medicare's new value-based purchasing (VBP) initiative is trying to realign some quality incentives, but still focuses just on individual hospitals instead of the larger epidemiological environment. While the Dutch have successfully responded to MRSA on a national basis, the fragmented nature of the US health care market (Elhauge 2010) makes this type of coordination more difficult.

Germ Shed Issues Within US Hospitals

MRSA Pollution from US Hospitals

MRSA pollution occurs when a health care institution does not prevent transmission. MRSA is a significant public health issue in the US (Wenzel 2007). A recent study by Klevens et al. found 94,360 invasive MRSA infections in the US in 2005, associated with 18,650 deaths (Klevens et al. 2007). Another study, published nearly simultaneously, found the MRSA infection rate to be higher (278,203) but the death rate lower (6,000) (Klein et al. 2007). While the data remains incomplete (GAO 2008), the medical community views MRSA as a large and growing public health problem: "Our findings suggest that *S. aureus* and MRSA should be considered a national priority for disease control" (Klein et al. 2007).

As MRSA emerged in the late 1970s, hospitals and other institutional providers turned to vancomycin as an effective treatment. Absent vancomycin, hospitals would have resorted to less effective treatments and implemented additional infection control measures. More patient deaths would undoubtedly have occurred, but a major MRSA crisis in the 1980s might have given the market enough signals to induce more antibiotic R&D in the following decades. The success of vancomycin dampened the need for other antibiotics in the 1980s and 1990s, much as methicillin dominated in the 1960s and 1970s. Vancomycin's success in the 1980s and 1990s contributed to the antibiotic incentive problem that many identify today (Talbot et al. 2006; Norrby et al. 2005; Wenzel 2004; Outterson 2010).[1]

Vancomycin's effectiveness in the last few decades permitted higher levels of MRSA pollution, both within the hospital as well as the larger germ shed. Vancomycin temporarily raised the optimal level of MRSA pollution and reduced the cost-effectiveness of both conservation and rival product R&D.

[1] If resistance stimulates innovation, then a corollary may be that a lack of resistance dampens innovation, but it dampens exactly the sort of innovation that we don't need.

Reimbursement Under US Medicare

Hospital Internal Incentives Under US Medicare

Hospitals can adopt control measures to reduce the internal and external levels of MRSA pollution. In economics textbooks, most of the cost of pollution falls on property owners downwind; a classic externality. MRSA pollution creates infectious disease externalities when infected patients are discharged or transferred, but a significant portion of the cost also falls on the hospital itself or its patients.

Let us therefore initially consider the internal costs. Ideally, infection control and antimicrobial stewardship would be financially rewarding for the hospital. Unfortunately, Medicare does not have a billing code for infection control or antimicrobial stewardship. These activities are cost centers for a US hospital, not direct sources of revenue. This is a first-order error if our goal is to promote long-term effectiveness of antibiotics. But perhaps the hospital can make a business case for antibiotic conservation, investing to reduce costs. An authoritative review of the medical literature concluded that:

> Effective antimicrobial stewardship programs can be financially self-supporting and improve patient care. Comprehensive programs have consistently demonstrated a decrease in antimicrobial use (22–36%), with annual savings of $ 200,000–$ 900,000 in both larger academic hospitals and smaller community hospitals. (Dellit et al. 2009)

This statement begs a question. If indeed the internal business case for antimicrobial conservation in hospitals is clear, then we should expect rational hospital executives to implement such programs. But the cost savings described above are illusory because they are based on "billed" charges (which are almost never actually billed) rather than actual Medicare reimbursement. The US reimbursement system is complex, with diverse financial incentives. The following paragraphs will examine the interaction between the Medicare reimbursement system and the direct internal savings in antimicrobial stewardship programs.

US hospitals contract with many health plan payors, both private and public. The most important payor is Medicare. Medicare's reimbursement system is important for two reasons. First, it is a very large program, constituting the largest single revenue source in most US hospitals (GAO 2008). Second, some private health plans have voluntarily adopted Medicare's reimbursement methodology, which magnifies its importance through a spillover effect (Dove 1994; Nichols and O'Malley 2006; Henderson and May 1983).

Until the early 1980s, Medicare reimbursed hospitals on a cost basis. Hospitals reported their allowable costs to Medicare, and those costs were paid, with an implicit mark-up for operating margin.[2] Over time, many policy experts recognized the inflationary effect of cost-based reimbursement. Hospitals lacked a financial incentive to cut costs. Rampant cost expansion followed (Scanlon 2006). For example, if a hospital had implemented an antimicrobial stewardship program dur-

[2] 42 C.F.R. § 405.402(a) (1982).

ing cost-based reimbursement, the "savings" would be illusory, since the reduced costs would also reduce revenues.[3] Worse yet, the hospital would lose the implicit mark-up on the foregone costs. This reimbursement system actually punished cost-saving measures such as antimicrobial conservation during the first decades of the Medicare program.[4]

For a time, the US Government fought back against higher hospital fees with increasingly complex rules for allowable charges.[5] These rules frequently resulted in protracted litigation over cost-based reimbursement. Rule articulation eventually proved both unwieldy and ineffective (Frankford 1993). In fiscal year 1983, Congress switched most US hospitals from cost-based reimbursement to prospective payment. The program is now called the inpatient prospective payment system (IPPS).[6] Under this system, the Centers for Medicare and Medicaid Services (CMS) organized hospital diagnoses and procedures into a list of diagnostic-related groups (DRGs), and announced a fixed price in advance for each DRG. The prices are based on a complex formula, which changes from year to year, and varies somewhat by geographical region and other factors such as wage costs.

Economic incentives are quite different under IPPS. Hospitals now benefit if they trim costs, since their payment is no longer tied to actual expenditures. This new reimbursement system has dramatically reshaped the US healthcare sector (Scanlon 2006). The Medicare reimbursement system now picks winners and losers on a macro level, favoring some procedures, services and patients over others. Profit variations occur both within and across DRGs. Variation within a DRG creates opportunities for favorable or unfavorable selection of patients. Admitting a sicker than average patient within a particular DRG may cause the hospital to lose money; admitting healthier than average patients has the opposite effect.

CMS has implemented methods that discourage adverse selection by providers. One such technique has been to divide single DRGs into narrower categories, which limits a hospital's ability to avoid high-cost patients. Another is to complicate DRGs by adding features such as co-morbidity modifiers, essentially splitting many DRG into multiple subgroups.[7] In general, the presence of MRSA in a patient can result in higher reimbursement under the DRG. The economic incentives favor treatment rather than prevention. Put another way, a highly successful antibiotic conservation

[3] If the cost-saving program generated spillover savings for patients reimbursed under other methodologies, then it is possible that the hospital would have improved its bottom line. To the extent that other payors followed Medicare's reimbursement model, these savings would disappear as well.

[4] This assumes that conservation programs were actually cost effective. If they raise net costs, then all of the incentives discussed in this section are inverted.

[5] *See, e.g.,*Social Security Amendments of 1972, Pub. L. No. 92-603, 86 Stat. 1329 (the "section 223 limits").

[6] Sec. 1886(d) of the Social Security Act.

[7] Medicare is now transitioning to the MS-DRG system with 258 sets of DRGs, each split into two or three subgroups depending upon the presence or absence of a "complication or comorbidity" (CC) or "major complication or comorbidity" (MCC). The total number of DRGs now exceeds 700.

program in a hospital will not generate additional Medicare revenue and will probably reduce revenues when less intensive co-morbidity modifiers are billed.

Medicare IPPS has other systemic effects on US hospitals. Variations across DRGs make some procedures and services more profitable than others. For example, the site of elective surgeries shifted dramatically since 1984, as the Medicare reimbursement system favored ambulatory surgical centers (ASCs) over hospital inpatient surgeries through a special payment rule. Many profitable surgeries migrated from typical inpatient settings to ASCs and specialty hospitals.

Finally, the boundaries between DRGs have encouraged unbundling services into different facilities in order to earn a new DRG. For example, early dismissal from a hospital might earn the full DRG, even if the patient was transferred to a post acute facility owned by the hospital. Hospitals responded to these financial incentives by discharging patients much more quickly, reducing US average length of stay below the Organization for Economic Cooperation and Development (OECD) median (Pearson 2009). Hospitals achieved this reduction in part by substituting post-acute care for inpatient services (Ashby et al. 2000). The federal government is concerned about these potential distortions and is acting to reduce them (MedPac 2007a), but new initiatives frequently lead to new unintended consequences (Werner et al. 2008). Each new adjustment adds layers of complexity to the Medicare reimbursement system. Some critics now resort to satire and mock Medicare's devilish details (Hyman 2006).

The IPPS is still biased in favor of diagnosis and treatment rather than conservation and prevention. Medicare has not created a reimbursable DRG code for hospital infection control efforts, antimicrobial stewardship programs, or special isolation procedures for MRSA. Medicare wants something that it isn't willing to pay for directly.

Hospital Germ Shed Externalities Under US Medicare

Hospital infection control efforts generate many positive externalities when infections and further resistance are prevented. Beneficiaries from avoided infection include the treated patient, other patients, hospital staff, other providers such as long-term care facilities, health insurance payors such as Medicare and commercial companies, and the community.

Epidemiologists and public health professionals attempt to maximize these positive externalities by reducing the spread of infectious disease. These benefits can accrue over time: conservation and infection control today may also improve the health of future patients, both through reduced transmission and the sustained availability of effective antimicrobial agents in future years (Laxminarayan and Malani 2007).

Competitive problems emerge when these positive externalities benefit other institutions in the market. For example, in a two-hospital town, if one hospital achieves excellent MRSA control, those efforts should reduce the number of MRSA colonized patients admitted to both hospitals. The first-mover hospital incurs costs for

infection control and a portion of the resulting benefits accrue to its direct competitor in the market. Likewise, infection control in a long-term care facility benefits the hospitals to which its patients are transferred, and vice versa. If these institutions are not under common ownership, infection control benefits other institutions, perhaps competitors. Antibiotic stewardship programs also generate positive externalities to society, above and beyond the direct savings to institutions. The economic problem is how to pay for these activities that benefit others. Germ shed management is therefore a collective action problem.

Medicare reimbursement currently treats these positive externalities and collective action problems with indifference, at best.[8] Consider IPPS reimbursement and infection control. Infection control requires meticulous attention to detail, including very thorough cleaning, barrier controls, and isolation. These activities are not free. Under cost-based reimbursement, hospitals may have earned a positive margin on infection control. Under IPPS, infection control is part of the cost structure and never generates revenues. These are odd signals in our reimbursement system.

At first glance, IPPS favors antibiotic stewardship programs. Reducing prescription costs will improve the hospital's operating margin. But this equilibrium is disturbed if the DRG is modified for infections. When patients acquire a nosocomial infection, the hospital may qualify for additional reimbursement for the complication or co-morbidity. Hospitals can earn additional revenues from nosocomial infections.[9] If the infection results in a readmission, even more revenue may accrue. The amounts involved are significant. For the average hospital-acquired infection, hospital costs were an additional $ 8,832 (Murphy and Whiting 2007). Infection with resistant bacteria can double hospital costs (French 2005).

Hospitals do not deliberately cause infections in order to increase revenue, but one unintended effect of the Medicare reimbursement system is to send mixed financial signals to hospitals about nosocomial infections. As Leah Binder of the Leapfrog Group testified to Congress, "We must assume that money is concentrated at hospitals with the *worst* record for hospital acquired infections. This perverse payment system impedes the implementation of critical quality processes" (Binder 2008). Certainly the hospital is not rewarded for creating these positive infection and resistance prevention externalities; it is possible that they are actually punished financially for helping others.

[8] In ordinary medical care, positive externalities include the continued contributions by the patient to society. IPPS doesn't reimburse for these social gains, although some prescription drug pricing in Australia and Europe takes this approach. Treatment of infectious diseases always generates the additional positive externality of epidemiology. While the calculation of the social benefits from health might seem remote and speculative, perhaps infectious disease control can make a stronger case for winning a slice of the epidemiological externality as reimbursement.

[9] Whether the additional revenues offset the additional expenses is another matter. It is also possible that a MRSA-free hospital would be more profitable, even without secondary diagnosis payments (GAO 2008) ("Hospitals may also incur some of the cost because they are not fully reimbursed for the cost of the extra care attributable to HAIs.").

Legal Barriers to Private Ordering

In an ideal Coasian world, hospitals could contract with the other institutions in their germ shed, allocating the positive and negative MRSA externalities through private ordering. Medicare explicitly makes many of these activities felonies through the fraud and abuse laws. In the US, it is illegal for a provider such as a hospital to make or receive a referral for many designated health services, if the two have a financial relationship. It would be illegal for a hospital to contract with an independent long-term care facility to coordinate infection control and antibiotic conservation generally if that contract anticipated any financial flow in either direction. In other words, Medicare prohibits private ordering to capture germ shed externalities.

US competition law also would look askance on contracts between horizontal competitors such as the hospitals in a germ shed. If the contract did not engage in naked price fixing or market segmentation it might not be *per se* illegal, but would still suffer potential review and liability for violation of US antitrust laws.

Congress must modify these laws if germ shed management is to occur through private contract. Otherwise, the coordinating mechanism must be Medicare. The following section explores that option, in all its complexity.

Creating Markets for Hospital Quality in the US Through Medicare

Medicare has not historically modified reimbursement for quality of care: both high quality and low quality care have been paid under the same DRG. Medicare has historically relied on professionalism, accreditation and the tort system to support minimum quality standards (GAO 2008). Medicare is currently experimenting with quality-related modifications to its reimbursement system.[10] Some of these modifications are important for infectious disease. Supporters characterize these changes as pay-for-performance (P4P) or VBP, creating a market for quality within Medicare. After describing the initiatives in some detail, we will evaluate their impact on MRSA germ shed externalities.

Paying for Reporting of Information

Assessing quality in Medicare depends upon timely and accurate data. In the Medicare Modernization Act of 2003, Congress ostensibly offered a carrot to hospitals,

[10] *See, e.g.,*Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates, 72 Fed. Reg. 47130, at 47200 (Aug. 22, 2007) (final rule); and FY 2009 Proposed Rule, 73 Fed. Reg. 23528, 23530 (April 30, 2008).

offering additional Medicare reimbursement (through the Annual Payment Update or APU) in exchange for reporting some hospital quality measures.[11] In reality, the offer was less carrot and more stick. The latest version reduces the APU by two percentage points for any hospital that does not "voluntarily" participate.[12] For larger hospitals, this reduction would be millions of dollars. The great majority of US hospitals participate, about 93% of the eligible hospitals (GAO 2008).

As with all things Medicare, the scope and complexity of reporting will increase over time. Originally, Medicare requested reporting of 10 hospital quality indicators.[13] Subsequently, Medicare has asked for comments on 26 additional "pay for reporting" datasets (MedPAC 2007a). The latest proposed rule adds 43 more for FY 2009.[14] Several of these datasets relate to infectious diseases, including a surgical infection dataset (MedPAC 2007a). This measure may lead to payment restrictions based on preventable readmissions (MedPAC 2007c). Some states simply require hospitals to publicly report certain hospital-associated infection information (Pennsylvania 2008). These data collection efforts are disjointed, but will form the basis for future policy (GAO 2008).

Reporting hospital-associated infections is a good first step towards identifying and quantifying MRSA pollution, but thus far no public database is tracking discharge of patients carrying MRSA or present on admission (POA) statistics from particular facilities. These specialized reports are the sort of information needed in order to better quantify germ shed pollution externalities.

Process Measures: Mandating Best Practices

The Medicare pay-for-reporting program includes three measures on infectious diseases. All three track processes rather than outcomes: (1) providing prophylactic antibiotics within 1 h of surgery; (2) selecting appropriate antibiotics to prevent surgical infections; and (3) stopping prophylactic antibiotics within 24 h after surgery. These statistics are available to the public on Medicare's website, as part of the program to provide better health care information to consumers. Many of the relevant accreditation standards from the Joint Commission are also process standards.

One weakness in the US health sector is measuring and rewarding inputs or processes rather than outcomes. Expensive inputs don't necessarily yield high quality care. The United States outspends the OECD and deploys the latest technology, but with modest comparative results.

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[11] Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003). The law was amended in Pub. L. 109-171, Section 5001(a) (2005), amending Section 1886(d)(3)(B) of the Social Security Act (42 U.S.C. section 1395ww(d)(4)). The first 10 hospital quality measures were proposed for reporting as of November 1, 2003.

[12] 42 U.S.C. sec. 1395ww(b)(3)(B)(viii)(I).

[13] *See* FY 2009 Proposed Rule, 73 Fed. Reg. 23528, at 23643 (April 30, 2008).

[14] FY 2009 Proposed Rule, 73 Fed. Reg. 23528, at __ (April 30, 2008).

Similar questions plague process-based reimbursement. Procedures may result in good outcomes, but sometimes they do not. A parallel controversy in drug development would be evaluating efficacy on intermediate clinical endpoints (such as lowering cholesterol) instead of actual clinical outcomes (reduced mortality from heart disease). Each of the three processes selected for the Medicare program appears to be reasonable and helpful, but their actual impact on patient health and antimicrobial resistance is not yet established.

Focusing on processes rather than outcomes runs the risk of teaching to the test. Hospitals may over invest in the listed processes, to the relative neglect of other actions that might yield better patient outcomes. For example, evidence suggests that hospitals achieve higher compliance with processes when measured (MedPAC 2003). Whether this is the best medical care available with the given resources is left unanswered at present. This question will turn on how carefully the processes were chosen, and how they are adapted to local conditions and constraints. In essence, some standards of medical care have been federalized when Medicare adopts a medical process by administrative procedure. This step represents a major change from the original promise that Medicare would not interfere in the practice of medicine. Nor is it likely to remain cabined in a niche of the Medicare program. The Government Accountability Office recently recommended that CMS adopt some of these standards into Medicare's Conditions of Participation (GAO 2008).

Outcomes Measures: Punishing Preventable Errors

The Deficit Reduction Act of 2005 introduced outcome measures related to reasonably preventable errors.[15] Congress instructed Medicare to identify reasonably preventable errors relating to at least two DRG codes. Medicare responded with enthusiasm, suggesting 13 errors for further study.[16] After a process involving the Centers for Disease Control and Prevention, health care industry lobbyists, Medicare Payment Advisory Committee (MedPAC), and others, Medicare identified six hospital-based errors in its FY 2008 Final Rule.[17] These six are sorted into two categories: "serious preventable events" and "reasonably preventable events." In the FY 2009 Proposed Rule, Medicare collectively refers to these errors as "hospital-acquired conditions" or "HACs."[18] A better term would be "hospital-associated conditions," as Medicare should not assume causation.

[15] Pub. L. 109-171, Section 5001(c) (2005), amending Section 1886(d)(4) of the Social Security Act (42 U.S.C. section 1395ww(d)(4)).

[16] Proposed Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates, 72 Fed. Reg. 24680 (May 3, 2007) (proposed rule).

[17] Proposed Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008 Rates, 72 Fed. Reg. 24680 (May 3, 2007) (proposed rule).

[18] FY 2009 Proposed Rule, 73 Fed. Reg. 23528, at 23529 (April 30, 2008).

Serious preventable events are also called "never events"—implying that they should never happen in a hospital. CMS identified three in the FY 2008 Final Rule: objects left in the body during surgery; air embolisms; and blood incompatibility.[19] In Medicare's view, these three errors are so fundamental that they should never occur. All three are in fact exceedingly rare. In FY 2006, CMS found just 764 Medicare beneficiaries with objects left during surgery, 45 who suffered from air embolisms, and only 33 with mismatched blood products.[20]

In the Medicare billing process, HACs may be coded as secondary diagnoses, and prior to this new rule, a hospital could receive additional IPPS revenues for the additional complication.[21] Whether an additional payment is made depends, in part, on whether the pairing of the original condition plus the secondary diagnosis qualifies for higher reimbursement as a MS-CC DRG. For example, the diagnostic code for leaving a foreign object in the body after surgery is ICD-9-CM code 998.4. That code qualifies as a "complication or comorbidity" (CC) that modifies the primary DRG for higher payment. Some serious preventable events are not listed as a CC, so Medicare has never paid additional reimbursement for those mistakes. When the code is not a CC, Medicare is already refusing to pay for the mistake, and there is no need to further adjust reimbursement.

The second category includes less fundamental errors that Medicare believes are "reasonably preventable." In the FY 2008 Final Rule, three were proposed: pressure ulcers (bed sores); hospital-associated infections (catheter-associated urinary tract infections); and *Staphylococcus aureus* bloodstream infection/septicemia. The *S. aureus* standard was dropped from the final rule. Beginning in October 1, 2008, Medicare will not allow the first two secondary diagnoses alone to qualify the DRG for a higher reimbursement level (MedPAC 2007a). The ICD-9-CM codes associated with these "reasonably preventable" errors will no longer qualify as a CC. Medicare subsequently re-proposed a quality measure for *Staphylococcus aureus* bloodstream infection/septicemia to begin in Fiscal Year 2015, and has also added other quality measures relating to infection control.

These changes may not make much financial difference. The Congressional Budget Office scored the statutory authority as having a modest budget impact over a decade (CBO 2006),[22] and MedPAC expects "the penalties to be applied in relatively few cases" (MedPAC 2007a). One reason is that if multiple CCs are present, Medicare only pays the upgrade once. The FY 2008 Final Rule blocks the six errors as CCs, but many patients have more than one secondary diagnosis. If at

[19] FY 2008 Final Rule, at 47201-02.

[20] FY 2008 Final Rule, at 47206-07.

[21] Technically, the hospital is being paid for the additional costs associated with treating someone after these events, such as re-opening the body to retrieve the lost object. It is possible that the hospital may have lost money on the secondary diagnosis, but P4P proponents argue that any payment reinforces poor quality.

[22] Recently, CMS has estimated the budget impact at $ 50 million per year. FY 2008 Proposed Rule, at 23915.

least one of them remains a CC, then reimbursement will remain unchanged at the higher level.

MedPAC suggests that Medicare apply a stricter rule to "never events," denying any CC upgrade, despite the presence of other CCs. MedPAC believes that Medicare has authority to create this rule administratively, without further Congressional action (MedPAC 2007a). The President apparently agrees, since his FY 2009 Budget proposed this stricter rule without seeking Congressional authorization.[23] Private payors are also adopting similar rules restricting reimbursement for "never events" (Binder 2008). This is another example of the spillover effect of Medicare reimbursement rules.

Fiscal impact will also be reduced as hospitals improve quality. More cynically, hospitals will also learn to adjust billing and coding practices to minimize reporting these errors as solitary secondary diagnoses. In any event, these quality incentives are the leading wedge in a much larger value-based purchasing initiative in Medicare. If the history of Medicare is any guide, these rules will significantly expand in scope and complexity over time. But these provisions are unlikely to lead to much litigation, because Congress blocked judicial review of the selection and revision of these codes.[24] Absent judicial review, we rely entirely on Medicare's administrative process for selecting particular processes and outcomes as "best practices" through the reimbursement system. The next section discusses potential weaknesses in allowing Medicare to be the final arbiter of evidence-based medicine.

Federalizing the Standard of Care?

Congress limited the Medicare penalties to "conditions that could reasonably have been prevented through the application of evidence-based guidelines."[25] If this is a patient-based standard, then Medicare would need to evaluate the facts and circumstances of every particular care episode and judge whether the HAC was both caused by the hospital and reasonably preventable through the use of evidence-based guidelines. If this were the case, then Medicare would be federalizing malpractice law for HACs. In the US, malpractice law has historically been controlled by the states.

But Medicare approaches these evidence-based guidelines from a population-health perspective. While each element of the reimbursement process relates to a particular patient, the decision on whether the HAC is reimbursable is made at an

[23] *See* FY 2009 Proposed Rule, at 23548.

[24] 42 U.S.C. sec. 1395ww(d)(7(B), as amended by Section 5001(c) of the Deficit Reduction Act of 2005.

[25] Pub. L. 109-171, Section 5001(c) (2005), amending Section 1886(d)(4) of the Social Security Act (42 U.S.C. section 1395ww(d)(4)).

abstract level, using population-based averages. Several questions are raised by this approach.

Evidence-based Guidelines

First, Medicare proclaims certain evidence-based guidelines as the standard of care, but they probably don't really mean it. For example, Medicare relies on CDC guidelines and the recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC). These are proclaimed as the standard of care in Medicare's value-based purchasing initiative:

> CDC produces evidence-based guidelines that serve as the standard of care in U.S. hospitals and guide the clinical practices of physicians, nurses and other providers…. Overall, these guidelines represent over a thousand evidence-based recommendations which, while large in number, address the vast complexity of modern medical care. All of the recommendations are prioritized according to the quality of evidence available to support them. (Wright 2008)

I doubt that Medicare intends to federalize malpractice by proclaiming a national standard of care. Medicare consulted these guidelines when it created the HAC list for reimbursement cuts. The intended meaning may be something closer to the following:

> These evidence-based guidelines should be consulted by physicians and institutions when making their treatment decisions as professionals, in consultation with the patient after informed consent. In some cases, evidence-based standards may disagree, or may not reach a clear conclusion. In others, best medical treatment will require departure from evidence-based standards. Medical care cannot guarantee positive outcomes, even when the standard of care was followed. **Nevertheless, Medicare will deny reimbursement for certain HACs, even if evidence-based guidelines were followed precisely**.[26]

Medicare discusses the guidelines because Congress required each identified HAC to have "evidence-based guidelines" demonstrating that the HAC was "reasonably preventable." Nothing in Section 5001 of the Deficit Reduction Act of 2005 requires the actual adoption of the referenced standards into medical practice.

Causation

A related question centers on causation. The FY 2008 Final Rule consistently uses the phrase "hospital-acquired."[27] The medical literature generally uses a more modest and less determinate phrase, "hospital-associated," "health care-associated," or

[26] Author's text. There is no exception in the MAC process for having followed the referenced standard of care.

[27] FY 2008 Final Rule, at 47201.

"community-associated" infections (Dellit et al. 2009). The differences between association and causation are significant, as any statistician will attest.

And yet the FY 2008 Final Rule denies reimbursement as if all HACs were "caused" by a preventable hospital error. Medicare denies reimbursement for HACs based on what is essentially strict liability. The medical community has raised this issue, but has done so ineffectively to date. Some commentators on the FY 2008 Final Rule "expressed concern that not all hospital-acquired infections are preventable and noted that sicker and more complex patients are at greater risk for hospital-acquired infections and complications."[28] In the preamble to the FY 2008 Final Rule, Medicare appeared to skirt the issue:

> Thus, we are only selecting those conditions where, if hospital personnel are engaging in good medical practice, the additional costs of the hospital-acquired condition will, in most cases, be avoided and the risk of selectively avoiding patients at high risk of complications will be minimized.[29]

Following the statutory mandate, CMS reviewed many evidence-based guidelines and found sufficient evidence for several conditions to be classified as "could reasonably have been prevented through the application of evidence-based guidelines."[30] Two HACs related to infections are:

> Surgical site infections. The groups and organizations stated that there were evidence-based measures to prevent the occurrence of these infections…[31]

> Catheter-Associated Urinary Tract Infections…. There are widely recognized guidelines for the prevention of catheter-associated urinary tract infections. Guidelines can be found at the following Web site: http://www.cdc.ncidod/dhqp/gl--catheter--assoc.html.[32]

Others were not chosen in the FY 2008 Final Rule, due to a lack on consensus on the causal evidence on preventability:

> Ventilator-associated pneumonias. The groups and organizations indicated that these conditions are currently measured and reported through SCIP. However, other organizations counseled against selecting these conditions because they believed it was difficult to obtain good definitions and that it was not always clear which ones are hospital acquired.[33]

> Pneumonia…. Some commentators mentioned that while prevention guidelines exist for pneumonia, it is not clear how effective these guidelines may be in preventing pneumonia.[34]

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[28] FY 2008 Final Rule, at 47200.

[29] FY 2008 Final Rule, at 47201. Note also the concern about adverse selection by hospitals and the ease with which CMS dismisses it.

[30] Pub. L. 109-171, Section 5001(c) (2005), amending Section 1886(d)(4) of the Social Security Act (42 U.S.C. section 1395ww(d)(4)).

[31] FY 2008 Final Rule, at 47201.

[32] FY 2008 Final Rule, at 47203.

[33] FY 2008 Final Rule, at 47201.

[34] FY 2008 Final Rule, at 47201.

> Clostridium difficile-associated disease (CDAD)…. While prevalence of this condition is emerging as a public health problem, there is not currently a strategy for reasonably preventing these infections.[35]

While the language is imprecise, the essence of Medicare's approach is as follows: For some diseases, evidence-based guidelines aren't yet proven to make a significant impact on patient outcomes. For others, the statistical evidence is better, and CMS will utilize those guidelines to select specific conditions to add to the HAC list. The act of denying reimbursement in any particular case is not an evaluation of whether any deviation from the standard of care occurred. The HAC may not have been reasonably avoidable, even with the best medical care. Nevertheless, Medicare will deny reimbursement.[36]

Medicare's approach to causation is revealed in the concept of "present on admission" or POA. Medicare will soon require hospitals to report whether CCs and MCCs were present on admission. This reporting originally did not affect reimbursement, but now POA is used to define when a CC or MCC is "hospital-acquired." Medicare will treat all CCs and MCCs as hospital-acquired unless they were reported as present on admission.

Several aspects of this rule seem unfair in the infectious disease context. The FY 2008 Final Rule proposed two infectious disease HACs: surgical site infections and catheter-associated urinary tract infections. Hospitals do not routinely screen for infections on admission, but they will either need to screen for urinary tract infections on admission or face reimbursement cuts if a catheter-associated urinary tract infection occurs. It is unclear what type of diagnostic screening will be helpful to establish POA for surgical site infections. It is also unclear when the test itself must be done. Perhaps hospitals can take samples on admission, but only complete the test if needed for billing purposes. That would save the hospital money on diagnostic testing, but would seem contrary to the purpose of testing.

The possible addition of MRSA and CDAD as HACs might require testing of every patient entering the hospital. This might be appropriate as an infection control measure, especially if it is adopted across an entire germ shed, but here it might be implemented as a reimbursement rule, untethered to best medical practice.

Creating New Diagnostic Codes for MRSA Infections

A third question concerns creating diagnostic codes to facilitate adding new conditions to the HAC list. Some HACs were not selected in part due to the absence of an appropriate ICD-9-CM code. In the MedPAC public meeting discussing the proposal, MedPAC Research Director Jack Ashby stated:

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[35] FY 2008 Final Rule, at 47201. Medicare is now overcoming its initial uncertainty regarding CDAD. The FY 2009 Proposed Rule included CDAD on the HAC candidate list. FY 2009 Proposed Rule, at 23558.

[36] The HAC rule does not include any exception for non-negligent care.

> Many were surprised that CMS did not include MRSA infections in this program, given the attention that these drug-resistant infections have received, but MRSA is not a CC or major CC so its presence alone would not result in additional payment and that pretty much disqualified it from the criteria of this program. But in addition to that, there is some question as to whether this infection can always be detected at admission. (MedPAC 2007b)

Ventilator Associated Pneumonia (VAP) was also excluded due, in part, to the absence of an appropriate ICD-9-CM code.

But this problem is easily corrected. Medicare controls the creation and modification of ICD-9-CM codes. The ICD-9-CM Coordination and Maintenance Committee has been working on a new code for VAP since at least 2004 (ICD 2004). Medicare discussed the need for a new code for VAP at the September 29, 2006 meeting of the ICD-9-CM Coordination and Maintenance Committee.[37] The new code was adopted a year later (ICD 2007). With the new code in place, Medicare has now added VAP to the HAC candidate list in the FY 2009 Proposed Rule, along with five other infectious conditions.[38] Many of these additions to the HAC candidate list deserve comment, but we will limit our attention to MRSA.

MRSA as a "Reasonably Preventable Condition"

In the FY 2009 Proposed Rule, Medicare announced that MRSA (and CDAD) were candidates for inclusion in the HAC list.[39] CMS is proclaiming that both conditions are "reasonably preventable through the application of evidence-based guidelines."[40] If that is indeed the case, then many physicians and hospitals are guilty of rank malpractice today. The history of these guidelines suggests that Medicare's conclusions are overly simplistic and ignores the many difficulties in effective implementation, including the lack of reimbursement.

Beginning in 1995, the CDC's Hospital Infection Control Practices Advisory Committee published recommendations to hinder the spread of vancomycin-resistant enterococcus (VRE) (CDC 1995). Twelve years later, they published interim guidelines regarding vancomycin-resistant *Staphylococcus aureus* (VRSA) (CDC 2007). Both are laudable summaries of the published Medline literature, but no mention is made of reimbursement. Recommendations include private rooms for VRE infected patients; dedicated devices for VRE areas; heightened cleaning, sterilization, and isolation protocols; and extensive lab testing of screening samples (CDC 2005). As of 2008, the CDC has 13 infection control and prevention guide-

[37] *See* FY 2008 Final Rule, at 47209.

[38] FY 2009 Proposed Rule, 73 Fed. Reg. 23528, 23556 (April 30, 2008).

[39] FY 2009 Proposed Rule, at 23558-60.

[40] Pub. L. 109-171, Section 5001(c) (2005), amending Section 1886(d)(4) of the Social Security Act (42 U.S.C. section 1395ww(d)(4)).

lines for healthcare-associated infections, covering 1,198 recommendations (GAO 2008). It is not clear which of these guidelines will eventually become standards for reimbursement, or what hospitals are to do when guidelines conflict or when the evidence base changes.

When MRSA is present on admission or discharge, we see germ shed externalities at play. Similarly, for CDAD, "more than one-half of the total burden of health care-associated CDAD cases have their onset in long-term care facilities" (McDonald 2007). So long as Medicare focuses on DRG reimbursement in single institutions, germ sheds will not be directly addressed.

Conclusion: Reducing MRSA Germ Shed Pollution by US Hospitals

If the level of MRSA pollution is too high within a germ shed, then hospitals and other institutions should invest in infection control and antibiotic stewardship on a regional basis. One key question that has been identified is reimbursement—who will pay? Medicare has focused on discrete providers and single episodes of care. The current and proposed rules extract financial penalties from hospitals for hospital-associated infections, even in the absence of negligence. Medicare's value-based purchasing plan is a Pigovian tax on hospital-associated infections, imposed without regard to causation or pollution in the germ shed.

When Medicare enshrines certain evidence-based guidelines as the gold standard, one concern is the federalization of the standard of care, which Congress has been historically loath to legislate.[41] Federalization suppresses the market for improving medical practice, with Medicare as the final arbiter. Medicare hasn't crossed this Rubicon yet, but may do so soon with the continued implementation of value-based purchasing.

As a more modest alternative, Medicare could create DRG codes for hospital infection control and antimicrobial stewardship, and set payment rates at a sufficient level to control resistance more effectively. To address germ shed externalities, some portion of the conservation DRG reimbursement could be placed at risk based on regional achievement of antibiotic resistance goals. To facilitate this process, hospitals could be financially encouraged to undertake joint infection control and conservation initiatives within the relevant hospital markets. Activities undertaken under these programs would be exempt from fraud and abuse and antitrust laws, permitting private coordination. Top-down national guidelines could then be replaced with the practices that worked best in each local community using local surveillance data, with decisions made by the relatively small number of hospitals, long-term care facilities and other institutions in the market.

[41] Yet there is no question after *Gonzales v. Oregon*, 546 U.S. 243 (2006) that it has the authority to do so under the Commerce Clause.

The key to effective management of MRSA pollution in a germ shed will be greatly improved and rationalized economic incentives for the various independent institutions, fostering coordination and cooperation within the germ shed.

Acknowledgments I wish to thank Marc Lipsitch of the Harvard School of Public Health for his assistance in the biology of resistance and Aaron Kesselheim, also at the Harvard School of Public Health, for discussions relating to non-patent coordination mechanisms for antibiotic conservation. This work is supported by research grants from the Public Health Law Program at the Robert Wood Johnson Foundation and the David Saul Smith Award from the Boston University School of Law.

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Required Actions to Control Antimicrobial Resistant Healthcare-Associated Infections

Inge C. Gyssens and Jos W. M. van der Meer

Abstract Resistance of microorganisms to antimicrobial drugs is a serious threat to patients that is increasing rapidly. With few new antibiotics in the research and development pipeline, prudent antibiotic use is the only option to delay the emergence of resistance. In this chapter we will focus on antimicrobial resistant healthcare-associated infections by reviewing hygiene and infection control measures and antimicrobial stewardship measures. Most interventions in both fields are effective in some settings and often in combination. Interventions at the hospital, such as installation and empowerment of infection control and antibiotic committees, translation of guidelines into hospital-specific antibiotic guides, and the support by ID consultants and/or antimicrobial stewardship teams are described. Both in the fields of hygiene and antimicrobial stewardship, national and international initiatives will be discussed.

Keywords Infection control • Hygiene • Antimicrobial stewardship • Quality of prescribing • Education • Guidelines

Introduction

Resistance of microorganisms to antimicrobial drugs is a serious threat to patients. The pace at which antimicrobial resistance occurs is increasing rapidly and becomes more frightening by the month. The emergence of multi-resistant bacterial strains like extended spectrum beta-lactamase-producing (ESBL), Gram-negative bacteria, and carbapenemase-producing *Klebsiella* species is of great concern, as these strains have entered health care facilities worldwide and have become among the most prevalent resistant strains in intensive care units in Southern European hospitals (Souli et al. 2008). Most recently, the totally resistant New Delhi metallo-betalactamase (NDM-1)-producing enterobacteriaceae has started its global spread (Kumarasamy et al. 2010). Interestingly, the problem has recently shifted from multi-resistant Gram-positive bacteria (methicillin-resistant *Staphylococcus aureus*

J. W. van der Meer (✉)
Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
e-mail: J.vanderMeer@aig.umcn.nl

I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8_14, © Springer Science+Business Media, LLC 2011

(MRSA) and vancomycin-resistant staphylococci and enterococci) towards these Gram-negative strains. This does not mean that the problem of resistant Gram-positive microorganisms has been tackled to any extent, it just means that the world has an additional burden of formidable magnitude. In addition to these bacterial problems, fungi have become resistant to the most widely used antifungal drugs, i.e., the azoles (Verweij et al. 2009).

Aroused by these gloomy signals, authorities and scientific communities have organized meetings and written reports during the past decade, but so far the impact of these have been quite limited (European Academies Science Advisory Council 2007; Gyssens 2008).

In this chapter, we will address the actions required to combat healthcare-associated infections caused by multi-resistant microorganisms. Although hospital hygiene strategies are a major component in the prevention of healthcare-associated infections, in this chapter we will focus on the issues concerning antimicrobial drug policy.

In the long term, new antibiotics are needed, as resistance will always occur. New vaccines and appropriate immunization policies will reduce the need for antimicrobial treatment. More research is needed as suggested by EASAC (European Academies Science Advisory Council 2007). However, as a gap of 10–15 years has been identified (European Centre for Disease Prevention and Control and European Medicines Agency 2009), immediate action is needed to conserve the power of the available arsenal.

Given the crisis proportions that have been reached regarding healthcare-related infections, stringent measures are now necessary. We propose that these should be taken at different levels:

1. At the level of the healthcare institution.
2. At the national level.
3. At the international level.

The measures we propose will be discussed below.

Healthcare-Associated Infections and Multi-resistant Organisms

The term ‘healthcare-associated infection’ (HAI) is used to refer to infections associated with healthcare delivery in any setting (e.g., hospitals, long-term care facilities, ambulatory settings, home care). This term reflects the inability to determine with certainty where the pathogen was acquired, because patients may have been colonized with or exposed to potential pathogens outside of the healthcare setting before receiving health care, or may have developed infections caused by those pathogens when exposed to the conditions associated with delivery of health care. In addition, patients frequently move among the various settings within the health care system (Siegel et al. 2007). The most important types of these infections are

pneumonia (health care associated pneumonia or HAP), urinary tract infections, intra-abdominal infections (e.g. pseudomembranous colitis), post-operative surgical site infections (SSI), and bloodstream infections related to the presence of indwelling intravascular catheters.

As these infections arise in a setting with high selection pressure exerted by antibiotics, they will often be caused by multi-resistant microorganisms and are relatively difficult to treat (Rice 2008). Frequently occurring examples of such healthcare associated resistant pathogens are MRSA, multi-resistant coagulase negative staphylococci (CNS), multi-resistant enterococci (such as VRE), and multi-resistant Gram-negative rods such as *Acinetobacter* spp, *Enterobacter* spp, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. *Candida* species have also become increasingly resistant to first line antifungals, such as fluconazole, and azole resistance of Aspergillus species is on the rise.

Epidemiology of Healthcare-Associated Infections

According to the European Centre for Infection Prevention and Control (ECDC), HAI prevalence ranges from 3.5–14.8% (average 7.1%) in the EU. The most frequent infections are UTI (on average 28%), followed by respiratory tract infections (25%), SSI (17%), bacteraemia (10%) and others. As HCAI occur in debilitated hospital populations (i.e. patients who have additional health risk factors, co-morbidities), it is not surprising that HCAI are leading to an estimated 37,000 attributable deaths and 16 million extra days of hospital stay in the EU (European Centre for Disease Prevention and Control (ECDC) 2008).

Recently it has become clear that HAI are not only confined to Western hospitals with sophisticated medical technology and invasive devices. HAI are increasingly reported from developing countries (Allegranzi and Pittet 2007). Resistance rates are also high; 46% of *Escherichia coli* strains and 51% of *Klebsiella* species strains were resistant to third-generation cephalosporins in a report on neonatal ICU-acquired infections in different countries (Zaidi et al. 2005). Apart from poor hygiene, sanitation and lack of resources, understaffing and low levels of staff training are responsible for poor infection control in non-Western countries.

Surveillance and Monitoring of HAI

Surveillance networks of HAI are of importance in order to monitor and compare institutions or countries. The first nosocomial infection surveillance network, the NNIS system, was established in the USA in the 1970s (Emori et al. 1991). Since then, many other countries have set up similar national surveillance systems using the infection definitions developed by the US Centers for Disease Control and Prevention (CDC). For example, in the Netherlands and Germany, HAI data has been

recorded within a national nosocomial infection surveillance system since 1996 ('PREZIES'—http://www.prezies.nl/) and 1997 ('KISS'—http://www.nrz-hygiene.de/) (Geubbels et al. 2000; Gastmeier et al. 2003). The surveillance methodology of PREZIES and KISS is comparable; their protocols are based on the American NNIS protocol using the definitions developed by the CDC. Participation is voluntary and confidential, the project is funded by the Ministry of Health and the network is coordinated centrally by a multidisciplinary team (Geubbels et al. 2000).

At the European level, the coordination of the Improving Patient Safety in Europe (IPSE) network for the surveillance of healthcare-associated infections (HAI) in Europe was transferred to ECDC. Monitoring of healthcare-associated infections in Europe is slowly extending with (in 2008) 17 countries having implemented surveillance of surgical site infections and/or surveillance of infections acquired in intensive care units following European standardized protocols of the HELICS network (Hospitals in Europe Link for Infection Control through Surveillance) (European Centre for Disease Prevention and Control (ECDC) 2010).

Parallel to surveillance of HAI, investigation of antibiotic use and resistance is also important to set targets for interventions and evaluation of their impact on the prevalence of resistance e.g. a reduction of % MRSA.

Hygiene and Infection Control Measures

In the combat against healthcare-associated infections, hygiene and infection control measures are essential components of our armamentarium. Here we will briefly review actions in this field that should and have been deployed to combat HAI. We will not discuss immunization policies, which have also been shown to limit the transmission of resistant microorganisms.

HAI arise by the acquisition of potentially pathogenic microflora that is constantly evolving in the milieu of the healthcare facility. Inanimate as well as animate objects are the sources of such organisms. Although colonization and subsequent infection with such microflora cannot be avoided completely, the efforts within the healthcare facility should be aimed at prevention by putting up barriers against transmission. Healthcare facilities around the world differ tremendously regarding the prerequisites for installing such barriers. Infrastructural constraints may have a strong impact. For instance, the nurse-to-patient ratio, distance between hospital beds, the number of beds in a hospital room, the quality of the cleaning and the distance from beds to hand-washing facilities may be important determinants (Beaujean et al. 2000). The availability of local guidelines on infection control and the presence of an infection-control service with dedicated personnel in the facility are important factors for successful hygiene policy.

Also of major importance are behavioral aspects. Is hand hygiene before and after patient contact a routine? Do the doctors as well as nurses practice it? (Doctors are notoriously non-compliant in this respect) A systematic review on observed or self-reported compliance rates showed an overall median compliance rate of 40%. Unadjusted compliance rates were lower in intensive care units (30–40%) than in other

settings (50–60%), lower among physicians (32%) than among nurses (48%), and before (21%) rather than after (47%) patient contact. The majority of the time, the situations that were associated with a lower compliance rate were those with a high activity level and/or those in which a physician was involved (Erasmus et al. 2010). Hand hygiene is not the only measure to avoid the spread of resistant microorganisms. Clean protective clothing, isolation routines for patients colonized or infected, avoidance of non-essential indwelling urinary and intravascular catheters, and meticulous care of wounds and intravascular devices all contribute strongly to optimal infection control. Small scale projects have shown implementation successes of interventions in infection control in resource-poor settings (Duerink et al. 2006).

At a national level, most countries could and should do more to enforce infection control. Is infection control being taught in nursing schools and in the medical curriculum? It is quite clear that there are major differences between developed countries in which lack of funds, priority settings, and commitment are playing a role. So far, campaigns promoting hand hygiene have been launched mostly by professional societies. A good example of such a campaign was the "Aktion Saubere Hände" that ran in Germany from 2008 till 2010 under the auspices of the minister of health http://www.aktionsbuendnis-patientensicherheit.de/?q=node/103. It is a pity that only a limited number of national authorities have launched their own campaigns. Fortunately, over the last several years a growing, but still limited number of countries have adopted international campaigns (see below).

An important international campaign was recently initiated by WHO under the slogan "*Clean Care is safer care, Hand washing Saves Lives*". Twenty-nine European Member States have pledged to "Clean Care". More than four thousand health care facilities in 40 WHO European countries signed on to "Save lives". By February 2011, 39 countries or areas have coordinated activities to promote hand hygiene in health care. WHO Patient Safety has initiated the informal network *WHO CleanHandsNet* for coordinators and leaders of such hygiene activities to share experiences (http://www.who.int/gpsc/tools/en). We feel that it is about time for more concerted action and more widespread participation of European countries within the WHO initiative! The WHO program provides support for implementing simple and applicable prevention measures and tools. Useful web-based improvement tools have also been developed at the national level, such as the UK's Clean Safe Care website (http://www.clean-safe-care.nhs.uk). One of the evidence-based changes that have successfully promoted hand hygiene is the systematic switch from hand washing to alcohol-based hand rub as the "gold standard" practice (Johnson et al. 2005). The WHO recommends making the use of alcohol-based hand rubs preferable to hand washing in most situations (World Health Organization (WHO) 2009). Finally, it is remarkable how the medical community worldwide is sloppy in conveying the message that the combat against HAI starts with proper hygiene and discipline. In online promotional or educational material, medical personnel, in particular physicians, are often depicted violating the recommendations of hygiene (Fig. 1). In this matter, cultural aspects (the long sleeved white doctor's coat) play an important role. Wearing (long) artificial fingernails has been associated with Gram-negative bacilli and yeasts (Hedderwick et al. 2000). In a study of surgical intensive care nurses, ring wearing increased the frequency of hand contamination

Fig. 1 Examples of pictures in advertisements and hospital brochures showing major violations against primary hygienic measures. **a** Open white coat, wristwatch, and long sleeves appearing from under the white coat. **b** Long sleeves appearing from under a white coat with short sleeves. **c** Open white coat with a necktie dangling in the bed and wristwatch. **d** Wristwatch, long sleeves of both shirt and white coat, and open white coat

with potential nosocomial pathogens (World Health Organization (WHO) 2009; Trick et al. 2003). Although only limited data is available on the actual transmission of resistant microorganisms following failure to respect primary hygienic measures, it is clear that wearing hand/wrist jewelry and long sleeved coats and shirts hamper the application of proper hand and forearm hygiene. In a recent French study, the risk factors linked to the wearing of jewelry in multivariate analysis were the type of medical center, the professional category (doctors wore more jewels than nurses), and older age (Vandenbos et al. 2011).

Antimicrobial Stewardship

The second major pillar for the control of antimicrobial-resistant healthcare-associated infections is antimicrobial stewardship. With this term we indicate the capacity to provide optimal antimicrobial prophylaxis and therapy. Stewardship encompass-

es all aspects of antimicrobial use, starting with the diagnosis of a presumed bacterial infection and its most likely causative organism, an estimate of the effectiveness of antibiotic therapy, the choice of the antibiotic, the choice of the right dose and route of administration, the de-escalation of treatment when the microbiology report is available, the switch to an oral treatment if possible and necessary, and stopping of treatment as soon as possible. Keywords in this context are “prudent use”, “streamlining” and “avoidance of selection pressure”.

Parallel with infection control practice, the quality of antibiotic prescribing differs greatly between countries. This has become clear from international comparative studies on antibiotic prescribing in a quantitative and qualitative fashion (Ansari et al. 2009; MacKenzie et al. 2005). In general, these differences in use are reflected by the magnitude of the antimicrobial resistance problems: the more (broad spectrum) antibiotics are used, the greater the prevalence of resistant microorganisms leading to a spiral of escalating broad-spectrum use. Thus, a leading question for this chapter is how to encourage antibiotic stewardship in a particular hospital, at national level, and then globally.

Determinants of Antibiotic Prescribing by Physicians

At the level of the physician in a health care institution, his or her prescribing habits are a result of cultural, contextual and behavioral factors. With regard to cultural factors, ‘cultural dimensions’ as proposed by Hofstede are likely to play a role. Hofstede’s concept teaches that in societies that tend to avoid uncertainty, more antibiotics are being prescribed than in societies with a lesser degree of uncertainty avoidance (Hofstede 2001). For a more extensive review see Hulscher et al. (2010). In addition, the tiered structure in a society also seems to translate into prescribing habits. In hierarchical societies, more antibiotics are being prescribed than in egalitarian societies (Deschepper et al. 2008; Kooiker and van der Wijst 2003). Interestingly, these cultural differences match quite well with religion; in the catholic (hierarchical) societies physicians tend to prescribe more antibiotics than in the predominantly protestant societies (Deschepper et al. 2001). Of course, such cultural differences pertain not only to the prescribing habits of doctors, but also to patients’ demands and expectations.

In addition to the culture that prevails in a country, the traditions of the various medical specialties may also matter. Although there are many prejudices and jests about differences between surgeons and internists, little is known on the impact of the medical specialty on the prescribing of antibiotics (Hulscher et al. 2010). Socio-economical factors, such as health care funding and more specifically, reimbursement of antibiotics, also play a role (Friis et al. 1993; Harbarth et al. 2002).

On the contextual level, the organizational structure within a health care facility has a clear impact (Schouten et al. 2005a; Dedier et al. 2001). A study on antibiotic consumption in a group of hospitals showed that working in a particular hospital was an independent variable for the antibiotic usage, explaining 43% of the observed variance (Shalit et al. 2008).

With regard to the behavioral factors influencing the prescribing process, there is still a lot to be learned. Behavior of individual doctors is shaped by the national, local and disciplinary cultural factors mentioned above. Intertwined with these are the prescriber's knowledge and attitude. A lack of knowledge of antibiotics and infectious disease may seriously hamper the quality of prescription. In this situation, the prescribing physician may prefer to err on the safe side, i.e., prescribing maximal broad-spectrum treatment, instead of making a well-informed guess. A negative attitude, based on a lack of agreement with protocols or guidelines, will also affect prescribing. Likewise, a lack of self-efficacy, a lack of outcome expectancy, and inertia may lead to poor prescribing (Cabana et al. 1999).

Knowledge of these determinants is helpful to understand why certain approaches to change inappropriate prescribing behavior are not effective.

Optimizing Antibiotic Stewardship at the Level of the Healthcare Institution

A good approach that is used in quality improvement of organizations is the Plan-Do-Check-Act (PDCA) cycle originally described by Deming (Deming 1986). It is an iterative four-step problem-solving process originally used in business process improvement. During the first activity, investigation of the current situation is initiated and a plan for improvement is formulated. The plan should contain clear aims. During the second phase, the planned improvements are executed in a controlled setting. During the 'check' phase, the result of the improvement is being measured and compared with the original situation and proven with the goals set. In the final phase, the results of the intervention are used to adjust the measures.

The first activity is to determine the magnitude of the resistance of major microorganisms (such as *S. aureus*, enterococci, *Escherichia coli* and other Gram-negative rods) on the one hand and the volume of use of various relevant antibiotics (3rd and 4th generation cephalosporins, carbapenems, quinolones and piperacillin-tazobactam) on the other hand. In addition to a survey of resistant bacteria, the occurrence of infections caused by fungi, such as *Candida* and *Aspergillus spp*. may be used as indicators of the consequences of broad-spectrum antibiotic use. The next activity would be to identify hospital departments with the highest prevalence of resistant microorganisms, and where most of the antibiotics are used. When the magnitude of the problem is clear, and the 'hotbeds' of resistance and/or high use have been identified, the quality of prescribing should be assessed in these problem areas. To this purpose, an algorithm for assessing the quality of an individual prescription (Fig. 2) is a very useful instrument. For the assessment, which is quite laborious, independent experts are needed. In addition, compliance with local, evidence-based guidelines can be determined. A pilot evaluation of five randomly selected cases will provide invaluable information on prescribing behavior and logistical bottlenecks to gather the necessary dataset.

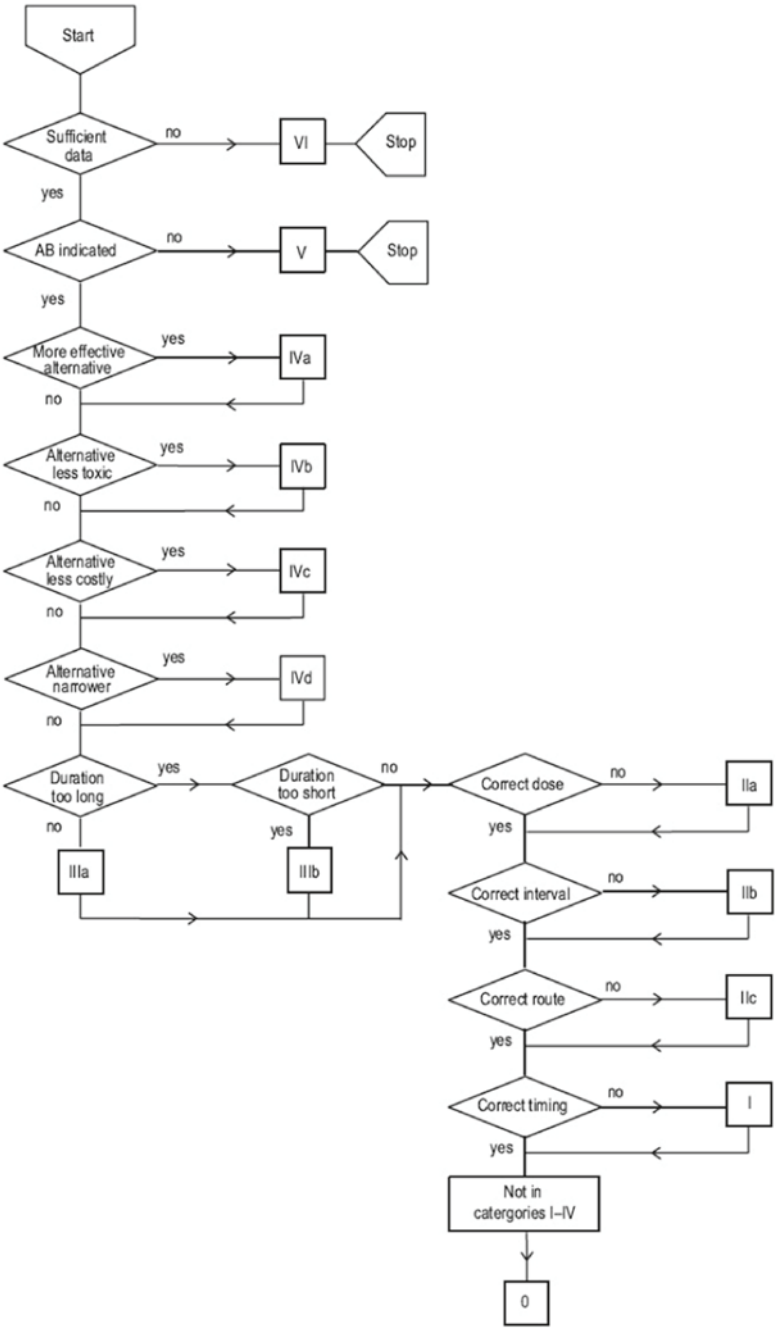

Fig. 2 Flow chart for quality assessment of antimicrobial drug prescription. An antibiotic prescription can be assessed as any of the numbers VI, V, or 0 or a combination of the numbers IV-III-II- I. (van der Meer and Gyssens 2001)

Table 1 Barriers to changing prescribing behavior in physicians

1. Knowledge	Lack of awareness
	Lack of familiarity
2. Attitude	Lack of agreement
	Lack of familiarity
	Lack of outcome expectancy
	Inertia
3. Behavior	External barriers

Peri-operative antibiotic prophylaxis is an unambiguous and straightforward area of antibiotic stewardship to start with. It is also the most rapidly rewarding topic for intervention (see below). However, finding major violations against evidence-based principles of prophylaxis or deviations from the guideline recommendations (e.g., inappropriate antibiotic, inappropriate timing, and/or too many dosages) does not guarantee that surgical colleagues will want to change their practice. A series of barriers may be in place. Some of these barriers relate to the national or regional culture, or to the system (hospital, reimbursement, staffing), but the most important ones are the barriers in physicians (Table 1). The barriers need to be lifted while formulating a plan for improvement. It is important to delineate clear goals. In the case of surgical prophylaxis these goals could be: 90% of the antibiotics should be given within 30 min before the first incision; 90% of the antibiotics should not be given after closure of the incision.

Before entering the 'do' phase, it is important to be clear about responsibilities of different stakeholders of surgical antibiotic prophylaxis. When we started our first project back in 1990, a key problem appeared to be that nobody felt responsible for the prescribing of the peri-operative antibiotics. The surgeons were supposed to do the operation and felt that they couldn't bother about the administration of antibiotics once they entered the operating theatre, whereas the anesthesiologists only felt responsible for the anesthesia procedure (Gyssens et al. 1997). We succeeded in convincing the anesthesiologists that they had a key role in the correct timing of the antibiotics. Using a motivated senior anesthesiologist as opinion leader was crucial in obtaining involvement of the department. The prophylaxis protocol was written in multidisciplinary collaboration and the logistics of the antibiotic administration were organized. One single antibiotic regimen was chosen for the majority of the procedures. Whether antibiotics were given was checked in a box on the daily operating theatre schedules, including the exact timing, and was carefully recorded on the anesthesia report. Since that time, checklists have become standard practice to improve operative procedures relating to patient safety. The 19 point WHO Surgical Safety checklist contains an item on the timely administration of antibiotic surgical prophylaxis (Haynes et al. 2009).

Do: When there is agreement about the proposed changes, they are implemented in a controlled setting, preferentially on a small scale. Many strategies to influence or control physician antibiotic prescribing have been studied (Table 2). These strategies include education, peer review with feedback, restrictive interventions, and financial incentives among others (Davey et al. 2005; Dellit et al. 2007). Antibiotic stewardship programs include antibiotic policy structures, tools, and dedicated per-

Table 2 Interventions to influence and control physician prescribing at the hospital level

1. Educational measures
Developing/updating local antibiotic guidelines
Clinical rounds discussing cases
Organizing an educational event with an authoritative opinion leader
Review and feedback of quantitative and qualitative data
2. Restrictive measures
Limiting the number of antibiotics on the hospital formulary
Formulary substitution
Categories of prescribing according to the background/seniority of the prescriber
Limited reporting of susceptibilities by the microbiology laboratory
Automatic stop orders
Antibiotic order form
3. Supportive measures
Consultancy service (microbiology, infectious diseases, pharmacy)
Therapeutic drug Monitoring (TDM) programs
Computer-assisted management programs

sonnel. Regarding structures, antibiotic committees in Europe and antimicrobial stewardship teams in the US (mostly consisting of an ID physician and a hospital pharmacist) (MacDougall and Polk 2005) conduct similar activities. Antibiotic committees should be multidisciplinary and include at least an infectious diseases physician, a (medical) microbiologist, a hospital pharmacist and clinicians from the major disciplines. The major tasks of an antibiotic committee are development of evidence-based guidelines that incorporate local microbiology and resistance patterns, regular monitoring of the local surveillance of resistance and use, identifying potential problem areas for audit and feedback, and other interventions including restriction. Antibiotic guidelines are intended to improve the quality of care, to support public health decisions, to diminish unwanted diversity of practice and to increase transparency (for the healthcare worker and the public). Guideline implementation can be facilitated through provider education and feedback on antimicrobial use and patient outcomes (Dellit et al. 2007).

Printed educational materials and educational conferences alone have had little effect on changing prescribing practices for antibiotics or other medications in the outpatient setting. More intensive and multi-faceted interventions are generally required. Face-to-face educational sessions provided by physicians or pharmacists sometimes known as academic detailing, have been successful in improving antibiotic prescribing practices. Participative physician feedback and multidisciplinary interventions have also been found to be effective methods to increase the judicious use of antibiotics and reduce costs (Davey et al. 2005).

Mixed results are found for almost all interventions and disparate results for any single tool. Although every intervention can show some successes, combinations of interventions have proven to be the most successful. Approaches successful in one setting may be less useful in a setting where barriers differ (Cabana et al. 1999). Returning to the example of interventions on peri-operative antibiotics, an intervention to improve prescribing would be obtaining compliance with a local guideline i.e.

that antibiotics are only given according to an agreed protocol for a defined list of surgical procedures. There should also be a list of frequently performed procedures that do not need antibiotic prophylaxis.

Check: During this phase the effects of the interventions are evaluated and it is assessed whether the goal that was set (e.g., the degree of compliance with a certain recommendation of the local guideline) is met. The evaluation allows checking underuse and overuse of antibiotics, timing and duration. The results are compared with the baseline situation.

Act: During this last phase, the results of the intervention are used to adjust the implementation measures. Were the goals reached? Should changes be made? Can procedures be simplified? How do we warrant sustainable compliance?

Finally, it should be possible to monitor the quality of antibiotic prescribing on a continuous base by using structure and process indicators. Quality indicators derived from an evidence-based guideline can be used. In a Dutch study, a systemic evidence and consensus-based approach was used to develop the first set of valid quality indicators to evaluate antibiotic use for lower tract respiratory infections in the hospital setting. A multidisciplinary panel reviewed and prioritized recommendations extracted from a recently developed national guideline. To test applicability in practice, feasibility, opportunity for improvement, reliability, and case-mix stability were determined for a data set of 899 hospitalized patients with lower tract respiratory infections (Schouten 2005b). Typical indicators for prophylaxis were: the percentage of patients receiving single dose prophylaxis, the percentage of patients to whom antibiotics were administered within 30 min prior to the first incision and the percentage of patients to whom antibiotics were given after closure of the incision.

Actions to Optimize Antibiotic Stewardship at the National Level

On 9 June 2009, the Council of the European Union issued a recommendation on patient safety, prevention and control of healthcare-associated infections (HAI). The recommendation invites Member States (MS) at national or regional level to consider and use the following advice:

- Implement standard and risk-based infection prevention and control measures in all healthcare settings
- Encourage adherence to the council recommendation by using structure and process quality indicators, as well as making sure the results of accreditation or certification processes are place.

As an example of national initiatives, the activities of the multidisciplinary Dutch Working Party on Antibiotic Policies SWAB are described here. SWAB was founded in 1996 as an initiative by the Societies for infectious diseases, medical micro-

biology and hospital pharmacists. Initiatives include making guidelines and recommendations available at the national level, postgraduate education, and surveillance of antibiotic use and resistance (SWAB 2010). Following advice by the Dutch Advisory Council on health research regarding the containment of antibiotic resistance in 2000, SWAB was appointed by the Dutch Ministry of Health, Welfare and Sports to coordinate the national surveillance of antibiotic resistance, in collaboration with the National Institute for Public Health and the Environment (RIVM) (currently: the Centre for Infectious Disease Control Netherlands, CiB) and granted structural funding procedures for the development of SWAB guidelines in 2005 (Prins et al. 2005). The new procedure includes the consultation of the concerned professional societies for delegating experts to the writing committee, and giving their members the opportunity to comment on draft guidelines. General practitioners are included on the writing committee to ensure the consistency between the guidelines for ambulatory care and hospitals. After final approval by the board, SWAB guidelines are posted on the SWAB website (http://www.swab.nl/guidelines). English versions are freely available from the site. Every hospital antibiotic policy committee in the Netherlands is offered the opportunity to edit the national version for local use. For a relatively small fee, SWAB provides a copy of the national version, in which adaptations can be made if local circumstances so demand, and this local version is again accessible through the internet, and downloadable on PDA. At the end of 2009, five out of eight university hospitals, and 14 general hospitals/hospital groups were using a local version of the national SWAB guide. Implementation of the guidelines in hospitals is studied in government-funded research projects (Van Kasteren et al. 2005; Schouten et al. 2007). Development of structure and process indicators is ongoing (Schouten 2005b; Hermanides et al. 2008). As most of the implementation projects are conducted as PhD programs (van Kasteren 2007; Schouten 2006), this national strategy results in a whole new generation of medical specialists with extensive training in antimicrobial stewardship. The impact of the surgical prophylaxis program has been assessed by the national surveillance system of HCAI prevalence and recognizes PREZIES in terms of surgical site infection rates (Mannien et al. 2006).

At postgraduate level there is only one option: changing behavior instead of creating behavior. The former is extremely difficult. Why are we trying to re-educate or change the behavior of doctors on the use of antibiotics when many among us are (also) responsible (in part) for their education in the undergraduate curriculum? A crucial component in a national antimicrobial stewardship program is an adequate undergraduate medical curriculum that contains modules of microbiology, clinical pharmacology with emphasis on the principles of prudent prescribing according to evidence-based guidelines, empirical therapy guided by national resistance surveillance, and streamlining therapy. As an example, the medical faculties of the Dutch Universities of Rotterdam and Nijmegen have included case histories in prudent prescribing and elective topics on antibiotic policy for second year students in their curriculum. Appropriate curriculum on antimicrobial stewardship is a joint responsibility of the academia and the ministries of Health and Education.

Actions to Optimize Antibiotic Stewardship at the International Level

Several organizations have deployed antimicrobial stewardship activities such as professional societies and governmental bodies. We list a few without trying to be complete.

The ESCMID Study Group for Antibiotic Policies

This group was created to provide a uniting European forum for those medical personnel and scientists actively involved in antibiotic stewardship at local, national and international levels. ESGAP aims to provide opportunities for improved cooperation and to establish links between existing networks of similar programs and those concerned with antibiotic resistance. ESGAP provides an opportunity for training in the appropriate use of antibiotics. Membership of ESGAP is open to those interested in good quality antibiotic prescribing at local, national and international levels, including representatives from the government or corporate bodies (http://www.escmid.org/esgap). A major activity is the postgraduate international education course named Antimicrobial Stewardship: Measuring, auditing and improving, which is conducted bi-annually before the European Conference on Microbiology and Infectious Diseases. Until now, six courses have been organized, training over 300 medical doctors, scientists, and clinical pharmacists over the past decade. ESGAP has also published its efforts of making an inventory of antimicrobial stewardship websites (Pagani et al. 2009).

The European Centre for Disease Prevention and Control (ECDC)

Major EC-funded research projects on the topic of Antimicrobial stewardship such as ESAC and EARSS have been under the umbrella of the ECDC since 2010. EARSS, actually called EARS-net, is a European-wide network of national surveillance systems, providing European reference data on antimicrobial resistance (European Centre for Disease Prevention and Control (ECDC 2010)). The recent ESAC point prevalence survey of antibiotic use in 20 hospitals in Europe has provided lessons about improvement targets. Overall, 30% of patients were prescribed antimicrobials; prophylaxis for surgery was continued for >24 h in 40% (Ansari et al. 2009). As shown by the report of the study from Scotland, the project provides national data that can be compared to Europe and identifies key areas for improvement. Only 57.9% of antimicrobials used were noted by investigators as being compliant with local guidelines. Recording indication in the medical notes is a recognized standard of good prescribing practice (Scottish Antimicrobial Prescribing Group 2009).

European Antibiotic Awareness Day is marked annually on 18 November. In 2010, the focus of the day was to promote prudent antibiotic use in hospitals with campaign communication materials made available on the ECDC website:http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx/.

The Center for Disease Control (CDC)

In 2010 the CDC started its campaign 'Get Smart for Healthcare' which focused on improving antibiotic use in inpatient healthcare facilities starting with hospitals and then expanding to long-term care facilities. The goal of the campaign is to optimize the use of antimicrobial agents in inpatient healthcare settings by focusing on strategies to help hospitals and other inpatient facilities implement interventions to improve antibiotic use. The CDC provides slides, fact sheets, and an annotated bibliography on the evidence base of outcomes among other tools on its website http://www.cdc.gov/getsmart/healthcare/. The CDC also collaborates with SHEA to develop simple implementation tools and with the Institute for Healthcare Improvement (IHI) and SHEA to develop a driver diagram with practical antibiotic stewardship implementation strategies

The Infectious Diseases Society of America (IDSA)

In 2004, IDSA published its report 'Bad bugs, no drugs: as antibiotic discovery stagnates a public health crisis brews,' and launched an advocacy campaign to spur government solutions. Now, 6 years later, the imbalance between the flow of the antimicrobial drug pipeline and resistance problems has only grown. In 2007, IDSA and SHEA issued guidelines for developing an institutional program to enhance antibiotic stewardship (Dellit et al. 2007). These guidelines provide an extensive blueprint for designing and implementing a successful stewardship program. Strategies were rated according to a grading system expressing the strength of the recommendation and evidence (see also Table 3). In June 2010, the IDSA launched the 10×20 initiative on its website; http://www.idsociety.org/10x20.htm, "to create a sustainable antibiotic R&D enterprise, which in the short-term can produce 10 new safe and effective antibiotics by 2020". In addition, the initiative aims to promote appropriate use of antimicrobials.

Alliance for the Prudent Use of Antibiotics (APUA)

This is a non-profit worldwide organization that was one of the first organizations (founded in 1981) that voiced concern with the rapid global increase in antibiotic resistance and proclaimed antibiotic stewardship. APUA has a network of affiliated

Table 3 Rated key strategies of antimicrobial stewardship. (Adapted from IDSA Antimicrobial stewardship guideline 2007 (Dellit et al. 2007))

Antimicrobial management team: multidisciplinary, compensated (AII-AIII)
Core activities of the team:
– Audit & feedback (AI)
– Formulary restriction/preauthorization (AII)
Optional activities:
– Guidelines/pathways (AI)
– IV/PO conversion (AI)
– De-escalation therapy (AII)
– Dose optimization (AII)
– Education (AIII)
– Order forms (BII)
– Cycling (CII)
– Combination therapy (CII)
Process measures
Outcome measures to determine the impact of antimicrobial stewardship on antimicrobial use and resistance patterns (B-III)
Health care information technology in the form of
– Electronic medical records (A-III)
– Computer physician order entry (B-II)
– Clinical decision support (B-II)

chapters in over 50 countries, supporting local healthcare workers with education and capacity building. For more information, see http://www.apua.org.

The World Health Organization (WHO)

Worldwide, WHO's actions to fight HAI are building on the WHO global strategy for containment of antimicrobial resistance (2001) (World Health Organisation (WHO) 2001) to further implement World Health Assembly resolution WHA51.17 on emerging and other communicable diseases (1998). The WHO's third Patient Safety Challenge on Antimicrobial Resistance was cancelled, due to lack of interest by funding countries and inspiring, charismatic leaders. However, at present, the WHO has chosen antimicrobial resistance as the topic for World Health Day 2011. On the 7th of April AMR will be put on the health agenda of 129 WHO member states.

The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR)

On 9 June 2009 the EU Council recommendation on Patient Safety and Prevention of Healthcare Associated Infections (HAI) was issued. It invites EU Member States

to adopt and implement HAI prevention programs at national, regional and healthcare institution levels. These programs should include diagnostic and therapeutic procedures (such as antimicrobial stewardship). ECDC has been mandated to support the implementation of these EU recommendations and will develop HCAI case definitions and infection control process indicators.

Additionally, in a recent US-EU joint declaration on November 3, 2009, it was decided, "To establish a trans-Atlantic task force (TATFAR) on urgent antimicrobial resistance issues. It is hoped that the task force will realize collaboration with related initiatives and organizations in Europe, USA & worldwide." TATFAR is made up of government representatives from the U.S. Department of Health and Human Services for the United States and from the European Commission, European Union agencies, and representatives of the EU member states holding three successive Presidencies. The objectives of the task force are to increase the mutual understanding of US and EU activities and programs relevant to the antimicrobial resistance issues identified in the declaration, to deepen the trans-Atlantic dialogue, to provide opportunities to learn from each other, and to promote information exchange, coordination and cooperation. The outcomes of the task force will include a proposal with suggestions for areas of future cooperation between the EU and the US to be presented at the EU-US Summit in 2011. ECDC provides the secretariat for the task force and publishes documents relating to the work of the task force on this website. http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Pages/index.aspx

Conclusion

Focusing on HCAI makes the urgency of AMR policies more visible to professionals. The patient safety approach is another opportunity to advocate prudent AB use. Until recently, AMR was poorly defined and viewed as a threat to the public and policy makers. To the drug companies it was a market opportunity.

At present, many infection control and antimicrobial stewardship initiatives are deployed at national and international levels, but the outcome in an individual healthcare institution greatly depends on the vision, responsibility and motivation of its healthcare workers.

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I. M. Gould, J. W. M. van der Meer (eds.), *Antibiotic Policies,*
DOI 10.1007/978-1-4419-1734-8, © Springer Science+Business Media, LLC 2011